DIGITALIS

Compiled and edited by

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Dedicated to the Physicians of Kansas and the Staff of our Medical School who have shared the philosophy that a physician's education is a continuing process and that the Faculty has an obligation to the physician in practice as well as to the medical student

Preface

THE UNIVERSITY OF KANSAS Medical School has recognized its obligation to its state and regional area to provide stimulating post graduate medical education This has been a major purpose of our school and a major obligation of our staff

In February 1956 the Medical School presented a two day post graduate program on the single subject of Digitalis The program was jointly sponsored by the School the Kansas Medical Society the Kansas Board of Health the Kansas Heart Association and the Kansas City Missouri Heart Association

Two hundred physicians were in attendance guest speakers were Dr Robert Batterman Dr Richard Bing Dr K K Chen Dr Santiago Grisolia Dr Bernard Lown Dr Aldo Luisada and Dr William Sodeman

The intent of this course as with the other Kansas post graduate courses was to present the subject from a practical viewpoint useful to the physician in practice but at the same time providing adequate physiological and pharmacological background

The material presented by the guest speakers and the scope of the panels offered an excellent coverage of the status of the *digitalis glycosides* their history pharmacology physiology experimental approaches toxicity and therapy were all well covered The content of the course was augmented by obtaining additional papers from Dr Ralph H Major Dr Meyer Friedman and Dr George Okita This book presents this collection of information

The contributors to the volume are representative of those working presently in this field in the United States Their individual papers and the panel discussion have been oriented toward the practical applied use of the drug and its background pharmacology

The editing of this volume has been facilitated by the generous help of Dr Sherman M Steinzeig Trainee National Heart Institute The secretarial burden was carried cheerfully by Miss Kathryn Calderwood I wish to thank both of them

E GREY DIMOND M D

Kansas City Kansas

Table of Contents

DIGITALIS

DIGITALIS

Doctor Ralph H Major presented in a beautiful and lucid manner the life of William Withering and the origins of digitalis in his book The Classic Descriptions of Disease *It seems particularly appropriate to begin this present volume with a reprinting of Doctor Major s essay*

Digitalis

WILLIAM WITHERING

DIGITALIS is without question the most valuable cardiac drug ever discovered and one of the most valuable drugs in the entire pharmacopoeia. The introduction of digitalis was one of the landmarks in the history of cardiac disease.

William Withering, who introduced digitalis into the practice of medicine, was born in Wellington, Shropshire, England, in 1741. His father was an apothecary-surgeon who enjoyed a good practice in Shropshire. William Withering received his first education at the school of his native town and later went to Edinburgh where he took the degree of M.D. in 1766. The following year he commenced practice in Stafford but does not seem to have been unusually successful since he wrote that his professional engagements scarcely produced on the average of six years one hundred pounds per annum. Presently he left Stafford and moved to Birmingham, taking over the practice of Dr. Small. In 1776 we learn that his practice had become considerable and his receipts increased to more than one thousand pounds a year. He gave free advice to the poor at his home on certain days and aided the poor and unfortunate in many ways. His extensive practice caused him to travel both day and night and during these trips he read and wrote. His carriage was equipped with a light so he could study while travelling along the countryside at night. His first published work was *A Botanical Arrangement of All the Vegetables Growing in Great Britain According to the System of the Celebrated Linnaeus with an easy introduction to the study of Botany*. He remained all his life an ardent student of botany and later became much interested in chemistry and mineralogy. In Birmingham he became a member of the Lunar

Reprinted from Ralph H. Major, M.D., *Classic Descriptions of Disease*, Springfield, Illinois, Charles C. Thomas, Publisher.

Society a scientific body so named because it met once a month and which numbered among its members such celebrities as Priestley and Watt

Withering s *Account of the Foxglove and Some of Its Medical Uses* was published in 1785 and immediately attracted great attention This work was the fruit of many years of observation and on its title page appears the appropriate quotation from Horace *Nonumque prematur in annum* (let it be suppressed for nine years) The year of its publication he was made a fellow of the Royal Society and received a diploma from the Medical Society of London This book of Withering is one of the classics of medical literature and greatly prized by collectors It sold when published for five shillings with the colored plate of the foxglove A copy sold in 1943 for $275 00

The use of digitalis in practice was condemned by Dr John Coakley Lettsom who enjoyed the largest and most remunerative practice in London Lettsom was a man of marked literary ability a skillful physician and a great philanthropist Lettsom on the recommendation of Withering had prescribed digitalis and in eight instances the illness had terminated fatally Among these patients was Charles James Fox the English statesman who was suffering from cirrhosis of the liver with ascites and in whom it had apparently produced a fatal effect Withering in a letter answering Lettsom s strictures complains that No one could compare Lettsom s choice of patients with my declaration of the fit and unfit or the doses he prescribed and the perseverance he enjoined, with my doses rules and cautions

Withering suffered for twenty years from bronchiectasis or possibly tuberculosis and died in 1799 age 58 He is buried in the Parish Church at Edgbaston his tomb being adorned with the staff of Aesculapius around which are entwined the serpent and the foxglove Withering lived to see digitalis admitted into the *Edinburgh Pharmacopoeia* and its merits generally recognized

Dr Erasmus Darwin the grandfather of Charles Darwin employed digitalis to good effect and sought to immortalize it in the following verses

Bolster'd with down amid a thousand wants
Pale Dropsy rears his bloated form and pants
"Quench me ye cool pellucid rills" he cries
Wets his parched tongue and rolls his hollow eyes
So bends tormented Tantalus to drink
While from his lips the refluent waters shrink
Again the rising stream his bosom laves
And thirst consumes him mid circumfluent waves
Divine Hygeia from the bending sky
Descending listens to his piercing cry
Assumes bright Digitalis dress and air
Her ruby cheek white neck and raven hair
Four youths protect her from the circling throng
And like the Nymph the Goddess steps along
O'er him she waves her serpent wreathed wand
Cheers with her voice and raises with her hand
Warms with rekindling bloom his visage wan
And charms the shapeless monster into man

BOTANIC GARDEN Part 2 Canto 2

AN ACCOUNT OF THE INTRODUCTION OF FOXGLOVE INTO MODERN PRACTICE *

As the more obvious and sensible properties of plants such as colour taste and smell have but little connexion with the diseases they are adapted to cure so their peculiar qualities have no certain dependence upon their external configuration Their chemical examination by fire after an immense waste of time and labour having been found useless is now abandoned by general consent Possibly other modes of analysis will be found out which may turn to better account but we have hitherto made only a very small progress in the chemistry of animal and vegetable substances Their virtues must therefore be learnt either from observing their effects upon insects and quadrupeds from analogy deduced from the already known powers of some of their congenera or from the empirical usages and experience of the populace

The first method has not yet been much attended to and the second can only be perfected in proportion as we approach to

* Withering William *An Account of the Foxglove and Some of its Medical Uses* Birmingham Swinney 1785 p 1 p 11

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mode of prescription but a circumstance happened which accelerated that event My truly valuable and respectable friend Dr Ash informed me that Dr Crawley then principal of Brazen Nose College Oxford has been cured of a Hydrops Pectoris by an empirical exhibition of the root of the Foxglove after some of the first physicians of the age had declared they could do no more for him I was now determined to pursue my former ideas more vigorously than before but was too well aware of the uncertainty which must attend on the exhibition of the *root* of a *biennial* plant and therefore continued to use the *leaves* These I had found to vary much as to dose at different seasons of the year but I expected if gathered always in one condition of the plant viz when it was in its flowering state and carefully dried that the dose might be ascertained as exactly as that of any other medicine nor have I been disappointed in this expectation The more I saw of the great powers of this plant the more it seemed necessary to bring the doses of it to the greatest possible accuracy I suspected that this degree of accuracy was not reconcilable with the use of a decoction as it depended not only upon the care of those who had the preparation of it but it was easy to conceive from the analogy of another plant of the same natural order the tobacco that its active properties might be impaired by long boiling The decoction was therefore discarded and the *infusion* substituted in its place After this I began to use the leaves in *powder* but I still very often prescribe the infusion

Further experience convinced me that the *diuretic* effects of this medicine do not at all depend upon its exciting a nausea or vomiting but on the contrary that though the increased secretion of urine will frequently succeed to or exist along with these circumstances yet they are so far from being friendly or necessary that I have often known the discharge of urine checked when the doses have been imprudently urged so as to occasion sickness

If the medicine purges it is almost certain to fail in its desired effect but this having been the case I have seen it afterwards succeed when joined with small doses of opium so as to restrain its action on the bowels

In the summer of the year 1776 I ordered a quantity of the

wards the discovery of a truly natural system but the last as far as it extends lies within the reach of every one who is open to information regardless of the source from whence it springs

It was a circumstance of this kind which first fixed my attention on the Foxglove

In the year 1775 my opinion was asked concerning a family receipt for the cure of the dropsy I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after the more regular practitioners had failed I was informed also that the effects produced were violent vomiting and purging for the diuretic effects seemed to have been overlooked This medicine was composed of twenty or more different herbs but it was not very difficult for one conversant in these subjects to perceive that the active herb could be no other than the Foxglove

My worthy predecessor in this place the very humane and ingenious Dr Small has made it a practice to give his advice to the poor during one hour in a day This practice which I continued until we had an Hospital opened for the reception of the sick poor gave me an opportunity of putting my ideas into execution in a variety of cases for the number of poor who thus applied for advice amounted to between two and three thousand annually I soon found the Foxglove to be a very powerful diuretic but then and for a considerable time afterwards I gave it in doses very much too large and urged its continuance too long for misled by reasoning from the effects of the squill which generally acts best upon the kidneys when it excites nausea I wished to produce the same effect by the Foxglove In this mode of prescribing when I had so many patients to attend to in the space of one or at most of two hours it will not be expected that I could be very particular much less could I take notes of all the cases which occurred Two or three of them only in which the medicine succeeded I find mentioned amongst my papers It was from this kind of experience that I ventured to assert in the Botanical Arrangement published in the course of the following spring that the Digitalis purpurea merited more attention than modern practice bestowed upon it

I had not however yet introduced it into the more regular

feeble his body greatly emaciated except his belly which was very large and upon examination contained a fluid The case had been considered as arising from worms He was directed to take the decoction of Digitalis night and morning It operated as a diuretic never made him sick, and he got well without any other medicine

Case IV

July 25th Mrs H of A near N between forty and fifty years of age a few weeks ago after some previous indis position was attacked by a severe cold shivering fit succeeded by fever great pain in her left side shortness of breath perpetual cough and after some days copious expectoration On the 4th of *June* Dr Darwin * was called to her I have not heard what was then done for her but, between the 15th of *June* and 25th of *July* the Doctor at his different visits gave her various medi cines of the deobstruent tonic anti spasmodic diuretic and evacuant kinds

On the 25th of *July* I was desired to meet Dr Darwin at the lady s house I found her nearly in a state of suffocation her pulse extremely weak and irregular her breath very short and laborious her countenance sunk her arms of a leaden colour clammy and cold She could not lye down in bed and had neither strength nor appetite but was extremely thirsty Her stomach legs and thighs were greatly swollen her urine very small in quantity not more than a spoonful at a time and that very seldom It had been proposed to scarify her legs but the proposition was not acceded to

She had experienced no relief from any means that had been used except from ipecacoanha vomits the dose of which had been gradually increased from 15 to 40 grains but such was the insensible state of her stomach for the last few days that even those very large doses failed to make her sick, and consequently purged her In this situation of things I knew of nothing likely to avail us except the Digitalis but this I hesitated to propose from an apprehension that little could be expected from any thing that an unfavourable termination would tend to discredit a medicine which promised to be of great benefit to mankind, and I might be censured for a prescription which could not be countenanced by the experience of any other regular practitioner But these considerations soon gave way to the desire of preserving

* Then resident at Lichfield now at Derby

leaves to be dried and as it then became possible to ascertain its doses it was gradually adopted by the medical practitioners in the circle of my acquaintance

Cases

CASES IN WHICH THE DIGITALIS WAS GIVEN BY THE DIRECTION OF THE AUTHOR

1775

It was in the course of this year that I began to use the Digitalis in dropsical cases The patients were such as applied at my house for advice gratis I cannot pretend to charge my memory with particular cases or particular effects and I had not leisure to make notes Upon the whole however it may be concluded that the medicine was found useful or I should not have continued to employ it

Case I

December 8th A man about fifty years of age who had formerly been a builder but was now much reduced in his circumstances complained to me of an asthma which first attacked him about the latter end of autumn His breath was very short his countenance was sunken his belly large and upon examination a *fluctuation in it was very perceptible His urine for some time* past had been small in quantity I directed a decoction of Fol Digital recent which made him very sick the sickness recurring at intervals for several days during which time he made a large quantity of water His breath gradually drew easier his belly subsided and in about ten days he begun to eat with a keen appetite He afterwards took steel and bitters

1776

Case II

January 14th A poor man labouring under an ascites and anasarca was directed to take a decoction of Digitalis every four hours It purged him smartly but did not relieve him An opiate was now ordered with each dose of the medicine which then acted upon the kidneys very freely and he soon lost all his complaints

Case III

March 15th A poor boy about nine years of age was brought for my advice His countenance was pale his pulse quick and

It is now almost nine years since the Digitalis was first prescribed for this lady and notwithstanding I have tried every preventive method I could devise the dropsy still continues to recur at times but is never allowed to increase so as to cause much distress for she occasionally takes the infusion and relieves herself whenever she chooses Since the first exhibition of that medicine very small doses have been always found sufficient to promote the flow of urine

I have been more particular in the narrative of this case partly because Dr Darwin has related it rather imperfectly in the notes of his sons posthumous publication trusting I imagine to memory and partly because it was a case which gave rise to a very general use of the medicine in that part of Shropshire

the life of this valuable woman and accordingly I proposed the Digitalis to be tried adding that I sometimes had found it to succeed when other even the most judicious methods had failed Dr Darwin very politely acceded immediately to my proposition and as he had never seen it given left the preparation and the dose to my direction We therefore prescribed as follows

R Fol Digital purp recent oz iv coque ex
   Aq fontan purae lb iss ad lb i et cola
R Decot Digital oz iss
   Aq *Nuc Moschat oz ii M fiat haust*
   2 dis horis sumend

The patient took five of these draughts which made her very sick and acted very powerful upon the kidneys for within the first twenty four hours she made upwards of eight quarts of water The sense of fulness and oppression across her stomach was greatly diminished her breath was eased her pulse became more full and more regular and the swellings of her legs subsided

26th Our patient being thus snatched from impending destruction Dr Darwin proposed to give her a decoction of pareira *brava and guiacum shavings with pills* of myrrh and *white vitriol* and if costive a pill with calomel and aloes To these propositions I gave a ready assent

30th This day Dr Darwin saw her and directed a continuation of the medicines last prescribed

August 1st I found the patient perfectly free from every appearance of dropsy her breath quite easy her appetite much improved but still very weak Having some suspicion of a diseased liver I directed pills of soap rhubarb tartar of vitriol and calomel to be taken twice a day with a neutral saline draught

9th We visited our patient together and repeated the draughts directed on the 26th of *June* with the addition of tincture of bark and also ordered pills of aloes guiacum and sal martis to be taken if costive

September 10th From this time the management of the case fell entirely under my direction and perceiving symptoms of effu*sion going forwards I desired that a solution* of merc subl corr might be given twice a day

19th The increase of the dropsical symptoms now made it necessary to repeat the Digitalis The dried leaves were used in infusion and the water was presently evacuated as before

strates two features the increase in the force of systolic contraction and the depression of the A V conduction

The mammalian heart responds in a similar manner Figure 2 represents systolic tension of the papillary muscle of the cat s heart reproduced from a publication by Cattell and Gold The muscle was immersed in Locke s solution and electrically stimulated at the rate of forty times per minute At arrow digitoxin was added Promptly the systolic tension was increased reaching a maximum at the end of seventy four minutes Figure 3 is a group of electrocardiograms of an etherized cat from Lead 2 during the slow continuous intravenous injection of a dilute solution of digitoxin After 54% of the lethal dose was administered the sinus rate was definitely slower than the initial and the P R prolongation became obvious After 66% of the lethal dose was injected the auricles and ventricles followed their independent rhythms Ventricular tachycardia with multiple foci of impulse formation started when 84% of the lethal dose had been infused Bundle branch block appeared at 90% of the lethal dose and the cat died from ventricular fibrillation This experiment illustrates two effects the depression of the A V conduction system and the slowing of the sinus rhythm The latter is attributable to the stimulation of vagal endings because double vagotomy or atropinization does away with this slowing '

It is common experience that a failing heart is more respon

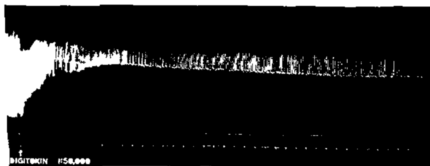


Figure 1 Tracing of the contractions of a frog s ventricle perfused with Ringer solution through the inferior vena cava At the arrow the perfusion was switched to digitoxin There is an occurrence of extra systoles 2 1 block and a systolic contracture

Pharmacological Basis for Digitalis Therapy

K K Chen *

William Withering an English physician learned of a secret recipe from a woman of Shropshire for the treatment of dropsy in 1775 It consisted of over twenty herbs but to Withering a competent botanist as well as a brilliant medical man it was obvious that digitalis was the active ingredient So he decided to use the leaves of digitalis not the whole recipe on his patients After ten years of studies he published his classical book *An Account of the Foxglove*

A perusal of this medical treatise reveals (1) Withering discovered digitalis by applying laymen s knowledge under a similar circumstance that Jenner discovered small pox vaccine (2) his discovery was made not by chance but by thorough knowledge of botany (3) Withering established the value of digitalis in dropsy by his careful study of 163 patients in a period of ten years and (4) he included in his book thirteen confirmatory reports from his colleagues and friends It is thus a perfect example of scientific research carried out some 180 years ago

About seventy five years after the discovery of digitalis the French and German physiologists pharmacologists and clinicians led by Vulpian emphasized the action of digitalis on the heart This is indeed the main and specific effect of the drug In the laboratory animals the action of digitalis on the heart can be broken down to at least three phases — (a) the increase of the force of contraction by the stimulation of heart muscle fibers (b) the stimulation of the vagal endings and (c) the depression of A V conduction Figure 1 shows a tracing of the frog s ventricle perfused with Ringer s solution through the inferior vena cava At arrow it was switched to digitoxin 'one of the active constituents of digitalis 'There was occurrence of extrasystoles 2 1 block and the tendency of systolic contracture This experiment demon

* From the Lily Research Laboratories Indianapolis Indiana

The heart rate is dramatically reduced by digitalis if auricular fibrillation accompanies heart failure It does not matter whether one believes in the circus movement theory or the ectopic focus theory since digitalis does not abolish the fibrillatory process What is important to the patient is that digitalis converts numerous feeble ventricular beats to a few forceful contractions The end result is the improvement of heart failure as measured by the reversal of its clinical signs

Aside from the cardiac action digitalis causes vomiting Fortunately the amount of the drug required for this reaction is

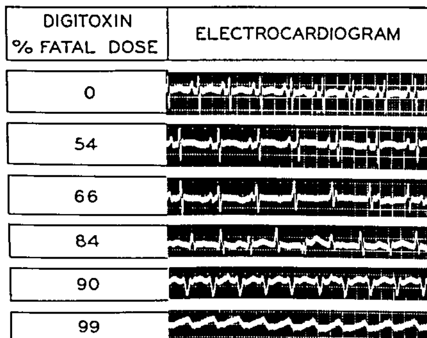


Figure 3 Represents a group of electrocardiograms from an etherized cat (Lead II) during slow continuous intervenous injection of a dilute solution of digitoxin After 54 per cent of the lethal dose was administered the sinus rate was definitely slower than initially and the P R interval prolongation is obvious After 66 per cent of the lethal dose is injected the auricles and ventricles follow independent rhythms Ventricular tachycardia with multiple foci of the impulse formation begins when 84 per cent of the lethal dose has been infused Bundle branch block appears at 90 per cent of the lethal dose and the cat died from ventricular fibrillation in the last strip

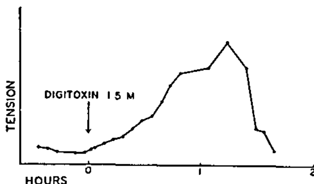


Figure 2 Represents the systolic tension of the capillary muscle of the cat s heart (reproduced from a publication by Cattell and Gold)· The muscle was immersed in Locke s solution and electrically stimu lated at the rate of 40 times per minute At the arrow digitoxin was added Promptly the systolic tension was increased reaching a maximum at the end of 74 minutes Illustration reproduced from *J Pharm Exp Thera* 62 116 1938 by Cattell and Gold Courtesy Williams & Wilkins Co

sive than a normal heart to the same dose of digitalis This is because of the fact that a normal heart is operating at an optimal efficiency and is less easily stimulated than the failing heart which is working under a physiological handicap and shows its relief when digitalis is administered To my second year medical students I am in the habit of making the subject simple and would tell them that digitalis is indicated as long as there are signs of heart failure What are the signs of heart failure? I place them in two columns of four items each

SIGNS OF HEART FAILURE (SEVERE)

Presence of	*Decrease in*
1 High venous pressure	1 Vital capacity
2 Cyanosis due to anoxia	2 Minute volume output
3 Chronic passive congestion	3 Rate of blood flow
4 Edema	4 Urine

The augmentation of the contractile force of the heart brings about a reversal of these signs This scheme serves as an introduction to their course in cardiology during the third and fourth year classes

bowels let it be stopped upon the first appearance of any one of these effects" Modern clinicians try to achieve digitalization and its maintenance by administering enough digitalis just short of causing untoward reactions which are loss of appetite nausea, vomiting diarrhea and evidence of A V block They realize that because their patients susceptibility to digitalis varies from one to another the dosage must be therefore individualized After the initial test doses it does not matter whether we start with 100 mg or 200 mg of digitalis three to four times a day for the first few days and continue with a maintenance dose of 100 mg per day or one half of the amount As long as the signs of heart failure are controlled without toxic manifestations the patient s interests are well served

When we prescribe digitalis we are giving the patient cellulose plant proteins lipids organic acids chlorophyll saponins and glycosides It is the last class of products the glycosides that contribute the digitalis action on the heart The glycosides are steroids coupled with natural sugars One hundred years after Withering s discovery of digitalis Schmiedeberg made a chemical analysis of the leaves and named one of the glycosides digitoxin This was further purified and crystallized It turns out to be the principal glycoside in both quantity and quality In 1940 Gold Cattell *et al* demonstrated the advantages of digitoxin in clinical use over the galenical preparations According to their work digitoxin is completely absorbed from the gastrointestinal tract while the active constituents in the crude form are absorbed approximately to the extent of 25% One biological unit of digitoxin can therefore accomplish what 4 biological units of digitalis powder will do Since digitoxin exerts its full effect upon swallowing a relatively smaller dose such as 0 1 mg can be used Such a small amount free from irritating impurities (saponins particularly) causes a minimum of local reaction mainly nausea and vomiting The pure principle thus can take the place of the crude drug much the same as morphine for opium and penicillin for the mold

Now if we let digitoxin represent digitalis we will have a slightly better idea of its distribution in the body and its elimination from it Like the crude drug digitoxin has a latent period of two to four hours and may take two to four days for full digitaliza

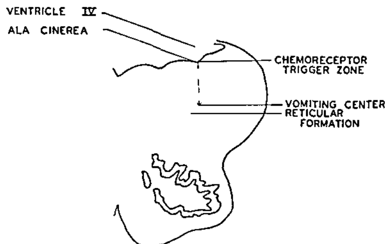


Figure 4 Indicates the suggested location of the chemoreceptor trigger zone lying on the dorsal surface of the ala cinerea in the medulla The impulse is then mediated to the vomiting center which is located in the lateral reticular formation (see text)

usually greater than that for the treatment of heart failure It is therefore avoidable clinically The mechanism of digitalis emesis is better understood now At one time it was said that digitalis directly acted on the vomiting center at another it was thought to be a reflex effect through the cardiac nerves Recent work by the neurophysiologists at Columbia University reveals that digitalis excites the chemoreceptor trigger zone which lies on the dorsal surface of the ala cinerea in the medulla (Figure 4) The impulse is then mediated to the vomiting center which is located in lateral reticular formation These areas were carefully located by direct application of the drug and ablation with microelectrodes

The expression of digitalis potency is much simpler today Although we retain the unit we can actually prescribe in metric weights Thus 1 U S P Unit is equivalent to 100 mg of digitalis powder or 1 cc of tincture of digitalis The U S P Unit is the same as the international unit Each batch of digitalis powder is biologically assayed in pigeons against the U S P standard

Withering's advice for using digitalis is Let it be continued until it acts either on the kidneys the stomach the pulse or the

digitalis restored adenosinetriphosphate and phosphocreatine which are energy rich metabolites At the same time the drug increases the oxygen consumption and glucose utilization of the heart Digitoxin tends to reinstate the molecular weight of myosin of the failing heart as measured by the ultracentrifuge My discussion can be accepted only as an elementary introduction to digitalis therapy

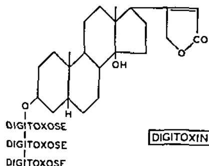


Figure 5 Illustrates the formula of digitoxin Notice the basic cyclo pento phenanthrene ring with the hydroxal group at C the sugar group at C and the lactone ring

tion It apparently takes time to saturate the tissues in order to attain the peak and plateau effect After absorption the glyco side appears in the blood gall bladder spleen and heart It is interesting that the unchanged digitoxin is not specially concen trated in the heart muscle Working with isotopic digitoxin Geil ing and his associates concluded that the liver was the principal organ for metabolizing this glycoside and the kidney the major organ of excretion The rate of elimination spreads over days thus accounting for its cumulative effect which is so well known The formula of digitoxin has several vulnerable points (Figure 5)

Hydrolysis certainly takes place because the residual struc ture without sugar has been identified in the urine The rich enzyme systems of the liver may inactivate the glycoside by at tacking the OH group at C_{14} by saturation of the double bond in the lactone ring or by the change of steric arrangements It is not inconceivable that saponification may take place upon long exposure to a pH greater than 7

Every year several hundred papers are published on digitalis and its related products Much fundamental information is added to our knowledge Heart failure can be surgically induced in experimental animals simulating clinical cases Numerous in vestigations deal with the action of digitalis at enzymatic and chemical levels For example on both normal and failing hearts

cept of muscular activity will become clear in subsequent paragraphs

Let us now proceed to modern studies on this problem The cell interior has a low sodium and a high potassium concentration whereas the ionic concentration on the outside of the cell is reversed During depolarization potassium moves outward during repolarization sodium moves into the cell The sodium and potassium concentration differences are built up during recovery by a cyclical process which absorbs potassium and extrudes sodium against the electrochemical potential gradient The amount of sodium extruded exceeds the amount of potassium absorbed In general only a trickle of ions leaks through the membrane passively but pores of the membrane open up when the membrane is depolarized and large ionic movements then take place as shown during the action potential Apparently the movements of ions across the cell membrane during the action potential or during depolarization are passive while the movements of ions across the membrane during recovery represent to a large extent an active transport Within recent years particularly due to the work of Hodgkins the separation between active and passive transfer of ions across the cell membrane has become apparent it has become likely that there is a coupled system which ejects sodium from the axon or probably from the muscle on one limb of a cycle and absorbs potassium on the other Thus if the potassium influx is abolished by removing external potassium the sodium outflow drops by an amount roughly equal to the original potassium influx Poisoning with dinitrophenol or cyanide greatly reduces the sodium outflow and also removes most of the potassium influx Cooling to 1 C has a similar effect The fact that the movements of ions across the membrane during the spike of the action potential are passive can be demonstrated by the fact that metabolic poisons do not prevent the rapid movements of the ion across the membrane during the passage of impulses

Consequently according to Hodgkins in addition to a permeability system there is a secretory mechanism driven by metabolism which ejects sodium and absorbs potassium against electrochemical gradients Conduction of impulses but not re

Some Physiological Actions of Digitalis

R J Bing M D

THE MECHANISM of the action of digitalis on the heart muscle still remains a mystery Clinical observations contribute little more to this problem It is likely that most of the advances in this field will come from fundamental studies of the structure and function of the cell It is for this reason that today s lecture will be primarily devoted to this aspect

I DIGITALIS AND IONS

The proteins of the muscle have the faculty of contraction The membrane of the muscle cell is responsible for the electrical activity The concentration of ions within the muscle cell differs from that in the surrounding medium in that the muscle cell is rich in potassium whereas the surrounding medium contains an excess of sodium Unquestionably the electrical impulse in the nerve and the action potential of the muscle is accompanied by a movement of ions across the membrane This was clearly stated many years ago by Bernstein and in the same year by Overton Bernstein suggested that nerve and muscle fibers are endowed with a surface membrane of special selective permeability and *excitable properties* This membrane has the *quality of being selectively permeable to potassium* ions and as a result of the unequal distribution of potassium on either side of the membrane *an electric potential difference is established* which is responsible for the action potential

Overton in the same year stressed the importance of the sodium ion in muscular contraction He showed that the excitability of muscle cannot be maintained without sodium in the surrounding medium and he concluded that the sodium ion must have a specific function thus impulse conduction and excitability is accompanied by a change between intracellular potassium and extracellular sodium ions How close he was to the present con

less than in ordinary aqueous solution This observation demonstrates that potassium certainly is not bound within the cell and that the ability to discriminate between potassium and other ions must depend upon a selective property of the cell surface or the membrane The situation with sodium is not very different because it has been found that potassium can penetrate more easily than sodium since the external concentration of sodium exceeds that of potassium about sixty times It appears then that the potassium ion has a much higher chance of entering the inside of the cell than has the sodium As was mentioned before steady concentration differences are maintained between inside and outside by an active energy spending process which is akin to active secretion of sodium which is continually at work in nerve and muscle fiber

Let us now consider the possible influence of digitalis on membrane permeability and possibly on active metabolic processes of the cell which regulate ionic exchange during the recovery period of the membrane

The effect of cardiac glycosides on the electrical excitability of isolated heart muscles can be demonstrated by microelectrode techniques Woodberry and Hecht using microelectrodes inserted into individual muscle fibers of frogs heart found that digitoxin lengthened and then shortened membrane action potentials Toxic doses brought about extreme shortening of repolarization The duration of depolarization was not affected However the amplitude of depolarization diminished with large doses of glycosides Resting potentials were not changed A similarity of the effect of strophanthidin to that of sodium lack on the intact heart was found by Daley and Clark A decrease in the sodium concentration in the medium in which the muscle fibers were soaked resulted in a loss of overshoot Furthermore the action potential became shorter with no change in resting potential Replacement of sodium chloride with iso osmotic saccharose resulted in similar changes Our observations on the effect of Cedilanid on mammalian heart muscle is similar to that described by Woodberry and Hecht on the frog heart muscle When muscle strips from dogs ventricles were suspended in tyrode solution to which Cedilanid in varied concentration had

covery can take place if the secretory mechanism is put out of action with inhibitors Finally sodium afflux and potassium influx are coupled but do not seem to be linked rigidly

It is as yet too early to point out the possible effect of these *modern concepts of membrane activity on the action of digitalis* However it is likely that glycosides influence the active metabolically driven movements of ions

What is known about the hypothetical structure of the membrane? The presence of a membrane is made likely by the fact that if we penetrate with a micro electrode into the interior of the cell a so called resting potential is obtained Apparently the interior of nerve and muscle fibers behaves like an ordinary electrolyte of somewhat lower conductivity than the surrounding solution but the cell surface contains a layer of high direct current resistance and large capacity It is obviously the different concentration in ions which is responsible for the membrane resting potential in that the conductivity of the inside of the cell is lower than that of the outside When we penetrate the surface of a heart muscle fiber with a microelectrode of 3 microns tip diameter the entry of the micromanipulated electrode into the fiber is indicated by a sudden drop of the potential at the tip of the electrode This leaves no doubt that the surface layer of the fiber must be the seat of a very high electric potential gradient

In addition at any given level of the muscle cell there are according to the English workers no measurable potential differences inside the fiber and the electromotive forces in resting and active nerves are developed wholly across the surface membrane Thus we have here the electrical evidence for a structure which separates the inside of the cell from the surrounding medium

Other more indirect proof for the presence of the membrane has come from an entirely different method of experimentation which bears close relationship to what was discussed in the first two paragraphs of this paper In referring to Hodgkins again there appears to be an exchange of ions across the membrane with a concentration gradient existing between the outside and the inside of the cell or the fiber Hodgkins and his associates were able to show that the ionic mobility and the diffusion coefficient of potassium inside the nerve fiber was only about 10%

less than in ordinary aqueous solution This observation demonstrates that potassium certainly is not bound within the cell and that the ability to discriminate between potassium and other ions must depend upon a selective property of the cell surface or the membrane The situation with sodium is not very different because it has been found that potassium can penetrate more easily than sodium since the external concentration of sodium exceeds that of potassium about sixty times It appears then that the potassium ion has a much higher chance of entering the inside of the cell than has the sodium As was mentioned before steady concentration differences are maintained between inside and outside by an active energy spending process which is akin to active secretion of sodium which is continually at work in nerve and muscle fiber

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been added a marked change was seen In the normal action potential three phases of repolarization are noticeable with an initial steep phase a plateau and a final steep phase Digitalis effect is characterized by shortening of repolarization which is primarily the result of the disappearance of the plateau and the final steep phase As a result the whole action potential shortens Signs of extreme toxicity consist of irregular spontaneous con tractions Fibrillation and arrest are not uncommon Charac teristically digitalis has no effect on the membrane resting potential

One may wonder at this point whether the clear demonstra tions of the effect of the cardiac glycosides on the membrane ac tion potential is not in disagreement with our hypothesis that digitalis glycosides act on the metabolic rather than on the excita tory phase itself One may venture the assumption that an action of the glycosides on the sodium influx or the potassium outflow during recovery may influence the action potential through a change in initial ionic concentration of the cell at the onset of the excitatory period

The strong binding power of the heart muscle to the glycoside was demonstrated in experiments in which it was shown that membrane action potentials of fibers which have been placed in tyrode solution containing Cedilanid maintain their digitalis effect when placed in Cedilanid free tyrode solution Theoretically the glycoside could have remained attached to the membrane or it could have penetrated the interior of the cell combining with the contractile proteins We therefore performed experiments to see whether or not Cedilanid had remained attached to the mem brane or whether it had penetrated the interior of the cell When muscle in tyrode solution containing Cedilanid was extracted in water for two to six minutes all mechanical and electrical ac tivity ceased When after that period of time the muscle strip was brought into contact with Cedilanid free tyrode solution action potentials demonstrating digitalis effect reappeared im mediately If it is assumed that water extraction destroys the membrane temporarily then the glycoside must have become fixed to the interior of the cell during soaking in water exerting its influence immediately upon restoration of the membrane in

tyrode solution On the other hand the glycoside may have been bound to the membrane itself which may have only temporarily lost its ability of depolarization and repolarization presumably through changes in permeability to sodium and potassium These experiments therefore gave us no answer to the question of where the digitalis binding to heart muscle fiber actually occurred All that can be said is that the electrical effect of the glycoside must be dependent upon ionic balances between the inside and the outside of the muscle fibers

Do cardiac glycosides influence the electrolyte balance of the whole heart in situ? The effect of therapeutic as well as toxic doses of digitalis glycosides on the electrolyte content of the whole heart has been a controversial subject Earlier studies by Harrison and his coworkers suggested that heart failure alone could influence the electrolyte content of the heart thus the right ventricular muscle of patients dying from pulmonary disease was found to have diminished potassium content while the left ventricular muscle did not When pulmonary and systemic congestion were present the potassium content of both ventricles was diminished Wilkins and Calhoun and others found decreased potassium and phosphorus concentration and increased sodium concentration in the ventricles of persons who had died of congestive failure

Although these studies suggested that heart failure itself may change the electrolyte content of heart muscle the possibility existed that digitalis may have been responsible for the observed electrolyte changes Earlier studies in this field have indicated that the potassium content of dogs hearts receiving toxic doses of digitalis was reduced while digitalis in therapeutic doses did not influence the concentration of potassium in the heart muscle Hagen found that therapeutic doses of Digilanid C caused a slight increase while toxic doses resulted in a marked decrease in potassium content of the perfused rabbit heart muscle In 1938 Wedd published a paper on the influence of digoxin on the potassium content of heart muscle His experiments were performed on the turtle ventricle which provided adequate control material He found that digoxin exerts a profound effect on the muscle contractility without causing significant changes in its potassium

content High concentrations of digoxin at times did result in marked potassium lowering but with that went great impairment of beat or even complete loss of excitability Apparently here as well as in some other more recent work the positive inotropic action of cardiac glycosides was not accompanied by changes in the electrolyte balance of heart muscle Wood and Moe using the heart lung preparation found good correlation between the magnitude of the efficiency increase of the heart and the rate of potassium mobilization from the heart muscle a finding which held true for both toxic and therapeutic doses of the glycosides They concluded that potassium mobilization from tissues of the heart may be associated with therapeutic digitalis action and is not merely a toxic manifestation of these drugs as some previous researchers have indicated

While previous data were primarily obtained on the heart in vitro or on muscle strips recent catheterization studies on the coronary sinus have made it possible to investigate the effect of cardiac glycosides on the electrolyte balance of the heart in a more physiological manner Using a powerful glycoside Acetyl strophanthidin it was found that the myocardial balance of potassium became negative and that of sodium positive immediately following the injection of the glycoside into dogs After twenty five minutes the opposite effect was recorded Less convincing results were obtained using K strophanthidin

We investigated this problem in patients with and without heart failure using the technique of coronary sinus catheterization Repeated blood samples were drawn from both the coronary sinus and the femoral artery during the control period and at ten minute intervals for sixty minutes following the injection of from 9 to 1 5 mg of Cedilanid No gross interference with the potassium or sodium balance of the human heart was apparent The only statistically significant finding was an increase in the potassium concentration in arterial and coronary sinus blood suggesting that Cedilanid in therapeutic doses causes potassium liberation primarily from extracardiac tissues

Despite these negative results a slight action of the glycoside on heart muscle balance of potassium and sodium cannot be completely excluded by these findings It is likely that there are

several factors which can influence the magnitude of the coronary arteriovenous potassium and sodium differences In the first place changes in coronary flow can alter the arteriovenous difference[1] Thus an increase in coronary flow reduces the arteriovenous difference However we had previously shown that digitalis glycosides do not influence the coronary blood flow Another factor is the speed with which potassium is released from the heart muscle Thus cardiac glycosides with very rapid action may lead to a demonstrable difference in the myocardial electrolyte balances The more rapid the loss of ions from heart muscle the larger will be their coronary arteriovenous differences[1] The final factor determining myocardial balances of electrolytes is the total quantity of potassium lost from the heart The more extensive the loss of the electrolyte from heart muscle the greater is the coronary arteriovenous differences It is likely that differences in the action of the various glycosides on the electrolyte balances of the heart are primarily the result of the speed with which potassium is released from the heart muscle This together with species differences may furnish the explanation for the difference *in action of cardiac glycosides on the myocardial potassium and* sodium balances

Much of what has been stated here has been based on experimental work relating electrolyte balances of the heart to the action of the glycosides In the following paragraphs views will be presented which relate these electrolyte changes to the contractility of the heart muscle Most of this work has come *from the laboratory of Szent Gyorgyi In order to comprehend his* concepts an understanding of certain fundamental aspects of the nature of the contractile proteins is essential Some of this will be discussed as we deal with the action of digitalis and contractile proteins directly According to Szent Gyorgyi the contractile matter is built of thread like thin and long protein particles myosin In the resting muscle the myosin is kept straight In the contracting muscle it folds The myosin particles are kept apart (in the straightened state) by two forces (1) their negative charges and (2) positive potassium ions which surround these charged protein particles Thus as Szent Gyorgyi expresses it the myosin particle is surrounded by a cloud of posi

tive potassium ions which keeps the myosin in a lengthened state and also keeps it in solution The greater the number of positive to negative charges the greater the repellent action Further more the thicker the positive ionic layer the greater the repellent action

It follows that in order for the muscle to contract or for the myosin particles to fold this repellent action of the potassium ion has to be eliminated *This is accomplished by a loss of potas sium* from the cell which as we have seen occurs during the ascending spike of the action potential As the muscle cell loses potassium the repellent charges are diminished and folding of the myosin molecules occurs Furthermore as potassium is lost from the cell myosin combines with another protein actin which also has been kept apart from myosin by the negative charges of the myosin and the positive charge of the surrounding potassium ions Thus as the excitation wave sweeps along the membrane *folding of myosin or contraction comes about by loss of potassium* and subsequent interaction of myosin with action with formation of the contractile protein actomyosin It follows that a loss of potassium is a favorable condition for contraction It is this con cept which is fundamental in Szent Gyorgyi s reasoning

Accordingly since potassium is lost during an individual con traction rapidly succeeding contractions should become more powerful since with short intervals between contractions potas sium has no chance to return into the cell to assume its guard position around the myosin molecules The staircase phenomenon is used by Szent Gyorgyi in support of his theories Baudich working on the isolated frog heart found that if the heart is arrested for some time the first beat after the pause is weaker than the last one preceding it If beats follow each other rapidly the contractions become stronger *Szent Gyorgyi explains this* phenomenon by stating that each single beat leaves a decreased potassium ion concentration behind which favors *contraction* During a long interval between beats this favorable condition deteriorates and potassium reenters the cell and the next contrac tion is weaker When the interval between beats is short potas sium remains outside the cell and contractions are stronger

Let us now return to the digitalis problem The first clue on

the action of cardiac glycosides on these mechanisms came when Szent Gyorgyi and Hadju found that if they replaced the Ringer solution in heart perfusates with serum the beat of the heart after a relatively long pause was as powerful as the preceding one According to the concept of Szent Gyorgyi serum contained a substance which kept potassium out of the cell This substance was found to be a sterol Digitalis also being a sterol had a similar effect

Szent Gyorgyi now continues his reasoning by stating that when the heart is damaged it seems to be unable to keep the potassium out The beneficial action of cardiac glycosides would then result from their ability to diminish intracellular potassium concentration This ingenious theory has a great deal of experimental backing but some of it is definitely still within the realm of *speculation* There is *for example* little evidence that potassium content of the failing heart is increased

II CARDIAC GLYCOSIDES AND CONTRACTILE PROTEINS

We have already heard that according to Szent Gyorgyi *myosin is negatively charged* but *that it is surrounded by positive* potassium ions which act as further repulsive forces Actin is the *other muscle protein which reacts with myosin* If an actin and a myosin particle meet in the presence of a physiological salt *concentration they unite to a complex actomyosin which* becomes partially discharged The uncontracted resting high energy *state is thus transferred by the movements of potassium ions in a* contracted low energy state The energy available for contraction *is contained in high energy* phosphate adenosinetriphosphate and it is with the myosin ATP complex that actin unites to form *actomyosin The actomyosin ATP formed in muscle under the* influence of excitation is spontaneously transferred into energy *poor contracted state The loss of energy can be used for* muscular work

We shall now *examine some fundamental* properties of actomyosin as they pertain to the action of cardiac glycosides In the first place *in the preparation of actomyosin extraction* of the heart muscle "brei with potassium chloride solution must be

carried out for at least twenty four hours It was first found in Szent Gyorgyi s laboratory that when muscle is extracted with a buffered KCl solution (6 mol) the mixture prepared by short extraction has a relatively low viscosity while after protracted extraction (over 24 hours) a very high viscosity ensues The highly viscous myosin was termed myosin B which now can be referred to as actomyosin the myosin of low viscosity was termed myosin A Apparently the prolonged extraction had added a new protein from the minced muscle which in combination with myosin leads to increased viscosity This new protein is actin which with myosin is responsible for the formation of actomyosin

The concentration of KCl and ATP profoundly influences the behavior of actomyosin Apparently in the presence of ATP at a low salt concentration there is complete dissolution and dissociation of actomyosin Then when the potassium chloride concentration is gradually increased an exceedingly intense precipitation occurs Instead of loose bulky floccules a dry looking granular superprecipitation is formed which settles rapidly to the bottom of the test tube occupying a small volume As we increase potassium chloride further suddenly complete dissolution and complete dissociation take place again The concentration of potassium chloride is extremely critical Szent Gyorgyi found that a difference of no more than 02 molar potassium chloride may change superprecipitation into dissociation It was already mentioned that the dissociated form possesses a low viscosity the precipitated form high viscosity An increased concentration of ATP makes the zone of superprecipitation smaller Thus the point of transition between the two states superprecipitation and dissociation depends on various factors Starting from the maximum of superprecipitation increased potassium chloride ATP magnesium pH or low temperature will favor dissociation Superprecipitation does not take place unless we have in the solution myosin actin ATP and salts After actomyosin has been formed by twenty four hour extraction ATP together with potassium chloride in the concentration used will keep the formed actomyosin in the dissociated form

How can the effect of cardiac glycosides on actomyosin be determined? Weber and his coworkers prepared the first acto

myosin thread which can be made either from purified natural actomyosin solution or from actomyosin which has been synthetized from myosin and actin Weber calls this actomyosin thread a thread model

Within recent years actomyosin threads have been made by other methods the best known probably being that of Hayashi of Columbia University Hayashi used the principle of surface spread actomyosin solution In this method the pure actomyosin is spread on the surface of a solution contained in a Langmuir trough By compression of this surface film actomyosin threads can be obtained which can be placed on a stationary hook The contraction of these fibers can be measured following addition of ATP Hayashi found that dilute potassium chloride appeared to fix the fiber at any length while an increase in salt concentration was necessary for elongation the presence of ATP was required for contraction Again we have here evidence of the importance of salt concentration for contraction with the conditions for contractions being ATP in low salt concentration for elongation ATP in high salt concentrations

There are certain disadvantages to these threads They are sticky and fragile and removing them from the bath suspending them on a hook and weighing them is a chore Furthermore the scatter of data obtained with this method is considerable This may be due to the fact that the actomyosin film spread on the surface of the trough does not represent a monolayer but surface precipitated layers of proteins with a certain degree of molecular orientation The reason for the fragility of the threads prepared with this method lies probably in the fact that the protein is partially denatured Such a denatured protein contributes nothing to contraction while increasing the fragility of the protein thread A final difficulty with this method lies in the measurement of shortening of these fibers This has been accomplished by observing the tip of the muscle strip with a horizontally aligned dissecting microscope This is not an objective recording

To overcome these various setbacks Dr Detth in our laboratory has introduced a method which resolves some of these difficulties In the first place the actomyosin threads need not be touched or transferred After compression the thread swims

on the surface of a subcompartment of the trough and can be attached to a torsion balance the movements and contractions of the thread are then observed by a null seeking device which permits continuous registration of the contractions of the actomyosin thread

Using this system the scatter of data is less the movements can be registered on a kymograph and tensions after loaded contractions and simple shortening can be recorded I might say here in passing that one of the most interesting facts which Dr Dettli s work has brought to light is that the contractility of actomyosin prepared from non beating hearts which have been removed from the body for one hour and left at room temperature is similar to that of a fresh preparation This opens a new field for the study of myocardial failure and the action of digitalis since it will permit the study of human actomyosin from autopsy material which has heretofore not been possible One of the greatest difficulties in studying the behavior of contractile proteins in myocardial failure is that actomyosin must be prepared from animal hearts in which failure has been artificially produced This may differ from the type of failure seen in the human The modification introduced by Dr Dettli will permit a study of the digitalized as compared to the non digitalized human actomyosin

There exists another "model of the contractile protein which is easier to prepare than the pure actomyosin thread I am referring here to the water glycerol extracted muscle which Weber calls the fiber model When skeletal or heart muscle is extracted in 50% glycerol for three days at 0 C followed by extraction from ten to fourteen days at −20 C and from these strips smaller 4 to 7 mm pieces are dissected a preparation is obtained which contracts upon the addition of ATP to the surrounding bath Neither epinephrine nor acetyl choline produce contractions The tension developed by the strip increases with rising ATP content of the bath Furthermore the degree of shortening of an isotonically contracting washed myocardial preparation is directly proportional to the logarithm of time Finally the speed of contraction expressed by its logarithmic slope decreases with rising tension and the work of the isotonically contracting muscle strip calculated per unit fiber is related directly to the tension

up to a certain point and decreases when the tension becomes excessive When these glycerol extracted heart muscle strips are stretched and the developing length is related to the tension as recorded by a strain gauge it is seen that a progressively larger rise in tension occurs with increase in length

To summarize then we have two tools at our disposal to study the action of cardiac glycosides on the contractile proteins One is the glycerol extracted heart muscle the fiber model and the other is the actomyosin thread or thread model

Let us examine the action of the cardiac glycosides on these two models We investigated the effect of Cedilanid on the mechanical activity of extracted heart muscle strips As described above the work of the extracted muscle strip increased with rising tension up to a maximum value and decreases as this tension is exceeded Prolonged periods of stretch leading to an increase in fiber length result in greater work performance of the extracted muscle Cedilanid has no effect on the work tension relationship of extracted heart muscle strips

Since the degree of shortening of extracted heart muscle was found to be directly proportional to the logarithm of time the slope of the contraction curve could be expressed as a function of the logarithm of time and the degree of shortening Using the slope as a function of the speed of contraction it could be shown that digitalized extracted heart muscle shortens at the same rate as the control Finally the effect of Cedilanid on the length resting tension relationship was investigated Since it has been maintained that the effect of digitalis is on the heart muscle directly expressing itself in changes in initial fiber length or in initial tenson the cardiac glycosides could conceivably influence the length resting tension relationship of extracted heart muscle by a relatively greater tension per increase in length However Cedilanid had no effect on the length tension relationship

So far our attempt to demonstrate the action of Cedilanid on the isolated glycerol extracted heart muscle strip had failed Entirely different results were obtained by Robb and Mallov These investigators found that ouabain made it possible for a thread to undergo greater shortening either with or without attached weight Furthermore the glycoside resulted in more rapid short

ening Robb and Mallov however used Hayashi s method in preparing the actomyosin threads the difficulties of this method have been pointed out in a preceding paragraph

To summarize In all likelihood cardiac glycosides influence the distribution of electrolytes between interior and exterior of the muscle cell An effect of cardiac glycosides on contractile proteins has been demonstrated in some preparations

III THE EFFECT OF CARDIAC GLYCOSIDES ON HEART MUSCLE IN CONGESTIVE FAILURE

In order to discuss the effects of cardiac glycosides on heart failure it is essential to dwell upon some of the metabolic aspects of congestive heart failure Accumulation of information regarding the metabolic processes of the heart muscle of human subjects with congestive heart failure has been hampered by a lack of suitable techniques for studying the problem in the environment under which it develops and in which it continues to progress Most previous studies on the metabolism of the failing heart have utilized either the isolated mammalian heart muscle preparation a pump oxygenator system or more recently intubation of the coronary sinus of animals While extremely valuable information obtained by such methods is not necessary applicable to human congestive failure or at least is subject to considerable misinterpretation when analogies are attempted Catheterization of the coronary sinus in man has now made possible a means of gathering data which would otherwise be unobtainable and of studying under physiological conditions with normal nervous and hormonal regulatory mechanisms some of the aspects of myocardial metabolism in congestive failure

Previous reports on the metabolism of the human heart using coronary sinus catheterization have shown that under normal resting conditions the myocardium extracts significant amounts of glucose pyruvate lactate fatty acids amino acids and ketone bodies from the coronary blood and that the extraction of each foodstuff is dependent chiefly upon its arterial concentration In the post absorptive state the heart derives on the average about 70% of its energy requirements from non carbohydrate material chiefly fatty acids but also amino acids and ketones

The ability of normal heart muscle to utilize whatever foodstuff is supplied can be demonstrated by raising the blood concentration of an individual substrate and observing the consequent increase in myocardial extraction

Considerably less is known about substrate utilization in congestive heart failure Studies were therefore undertaken in this laboratory which could be used to aid in resolving the following problems (1) is there any difference in the amount of oxygen consumed by equal weights of normal and failing human heart muscle? (2) Is the failing heart deficient in its ability to utilize any of the basic foodstuffs consumed by the normal heart (3) Is there any evidence of anaerobic myocardial metabolism in congestive heart failure (4) Is the reduced efficiency of the failing heart due to deficient energy production or inefficient energy utilization? Some of these questions have direct bearing on the problem of digitalis effect on the failing heart

To accomplish at least a partial answer to these questions twenty patients with congestive failure of common etiology were studied We compared the data with similar findings in two control groups one consisting of subjects with entirely normal hearts and the other of patients with known cardiac disease but without congestive failure

Cardiac output and respiratory quotient of the heart Cardiac output was diminished in the failure group The mean respiratory quotient of the heart averaged 75 indicating that the energy requirements of the heart in the postabsorptive state are met chiefly by non carbohydrate foodstuffs No difference between the failing and non failing hearts was found

Coronary flow in the congestive failure group was slightly diminished but not significantly so The coronary arteriovenous oxygen difference was slightly but not significantly above that of the control group The oxygen usage per gram of myocardium was the same in congestive failure as in the normal

Substrate Utilization The overall pattern of foodstuffs utilized by the myocardium was not altered in the presence of congestive heart failure

Although these findings were on the whole negative some conclusions can be drawn from them The first applies to our

question Is there any difference in the amount of oxygen consumed by equal weights of normal and failing human heart muscle? The fact that the oxygen usage of the failing heart is identical with that of the normal heart indicates that myocardial energy production is not grossly interfered with in failure

As to the next question Is the failing heart deficient in its ability to utilize any of the basic foodstuffs consumed by the normal heart? This question can also be answered in the negative since we found normal utilization of the essential foodstuffs by the failing heart

The third question Is there any evidence of anaerobic metabolism in congestive heart failure? This question is more difficult to answer but an evaluation of lactate metabolism in patients with congestive failure and consideration of some of our previous work on experimental animals should permit an estimate of the possible role of anaerobiosis as a means of energy production in heart muscle

It has been observed that the arterial lactate concentration in some patients is elevated Our data also show a considerably increased arterial lactate concentration in our patients with congestive failure This suggested that tissue oxygenation is adequate for optimal aerobic energy production The question arises whether the heart participates in anaerobiosis in congestive failure In contrast to skeletal muscle normal cardiac muscle is apparently able to increase its aerobic metabolism sufficiently to perform increased work within physiological limits without resort to glycolysis Numerous observers have reported studies in experimental animals demonstrating that the myocardium does not contract a significant oxygen debt during increased cardiac work However it is likely and this seems to be the crux of the matter that the apparent difference between heart and skeletal muscle is quantitative rather than qualitative since under conditions of marked *hypoxia the lactate concentration of the coronary sinus* blood may exceed that of arterial blood indicating the occurrence of significant glycolysis This is for example the case in ventricular fibrillation and in myocardial infarction where glycolysis in heart muscle occurs

From considerations of the glycolytic process in skeletal mus

cle and from the behavior of lactate metabolism in the ischemic myocardium it is inferred that if anaerobiosis occurs in cardiac muscle of human subjects with cardiac failure it should be detected first by diminished extraction of lactate from coronary blood A review of our data indicates that such a process may actually occur in some of the patients with congestive heart failure For example although the arterial lactate concentration in failure is significantly increased myocardial extraction of lactate is not elevated Analysis of our individual observations demonstrate that diminished lactate extraction is evident chiefly in those subjects with the higher arterial levels In contrast to the results in patients with heart failure subjects in the control group show no decreased lacate extraction at higher arterial levels There is therefore suggestive evidence for myocardial anaerobiosis in some of the patients with congestive failure It is unlikely however that the amount of energy liberated by glycolysis is sufficient to alter substantially the total energy production of the heart as calculated from oxygen consumpion

The conclusion therefore can be reached that the failing heart is deficient in its ability to utilize energy for effective muscular contraction even under basal conditions since the mechanical work performed is normal or decreased

It is logical then to start with the working hypothesis that in congestive failure glycosides will aid to reestablish the link between energy production and utilization Catheterization of the coronary sinus has enabled us to examine the effects of cardiac glycosides on the cardiac pump itself rather than studying the effects of these drugs on the pump's action in the form of cardiac output and pressure It has been well known for many years that cardiac glycosides increase the cardiac output and consequently the left ventricular work We found that digitalis has no effect on the oxygen consumption and therefore the increase in cardiac efficiency resulting from their administration is entirely the result of increased left ventricular work These findings do indicate that cardiac glycosides act to reestablish the link between aerobic energy consumption and the effective work of the heart The mechanism by which this is accomplished is unknown but the preceding paragraphs suggest that this may be through direct action

of the glycosides on the contractile proteins If this is correct then digitalis should have no action on myocardial metabolism This problem will be discussed in subsequent paragraphs

The various glycosides differ very little except in time of onset and persistence of action Lanatoside C the preparation which we used in our study is a purified derivative of digitalis lanata which can be given intravenously With average digitalizing doses of 1 2 to 1 6 mg the so called vagal effect usually appears within fifteen to twenty minutes reaching a maximum in about forty minutes If the glycoside has an action on myocardial metabolism this should become apparent within that period of time We selected twelve undigitalized adult patients for our study Some of them had no heart disease others were in congestive failure or had hypertensive or rheumatic heart disease Cardiac metabolism was studied by using the method of coronary sinus intubation

No significant changes in the respiratory quotient or the extraction of foodstuffs by the heart was noticed The only significant effect was a slight elevation of the percentage glucose extraction This negative effect of Cedilanid on carbohydrate metabolism in the intact human heart contrasts with the results of Wollenberger This investigator found in studying the action of ouabain on respiration of heart slices in the Warburg apparatus that the glycoside accelerates the oxidation of glucose and lactate This action accounted for the simultaneous increase in respiratory activity with the acceleration of glucose oxidation exceeding in proportion that of the oxygen uptake Our results demonstrated only a slight elevation in percentage glucose extraction without any change in myocardial oxygen utilization Since myocardial lactate utilization remained unchanged a digitalis induced shift from a glycolytic to a largely respiratory metabolism of carbohydrates as suggested by Wollenberger appeared to be unlikely in the human heart under the conditions of our tests

The finding that the cardiac glycoside produced no significant changes in myocardial oxygen consumption or in total foodstuff utilization confirms that the improvement in work capacity of the failing heart induced by the glycoside must be the result of the

action on energy liberation or more specifically on the contractile protein of the failing heart muscle directly

I conclude by quoting from Claude Bernard's *An Introduction to Experimental Medicine* an excerpt which I hope stresses certain pitfalls of clinical investigation in general

> In the part of the investigation devoted to nutrition Bidder and Schmidt described a very notable experiment perhaps one of the most laborious ever performed From the point of view of elementary analysis they kept a balance sheet of everything taken in and given out by a cat during eight days nourishment and nineteen days fasting This cat was in a physiological condition of which they were unaware She was pregnant and she had her kittens on the seventeenth day of the experiment In these circumstances our authors considered the kittens as excretions and calculated them with other eliminated materials as a simple loss of weight

Claude Bernard then continues

> I believe that these interpretations should be rectified when trying to define such complex phenomena

Another quotation

> Chemical averages are often used If we collect a man's urine for 24 hours and mix all this urine to analyze the average we get an analysis of a urine that simply does not exist for urine when fasting is different from urine during digestion A startling instance of this kind was invented by a physiologist who took urine from a railroad station urinal where people of all nations pass and who believed he could thus present an analysis of the *average* European urine! So in physiology we must never make average descriptions of experiments because the true relations of phenomenon do not appear in the average when dealing with complex and variable experiments we must study the various circumstances and then present our most perfect experiment as a type which however still stands for true facts

The Fate and Deposition of Digitoxin in Animal and Man

MEYER FRIEDMAN M D *

INTRODUCTION

PRIOR to the last decade any exact quantitative information concerning the fate of a digitalis glycoside in the body of man or animal was non existent This of course was due to the fact that the drug was effective in tissues when present in sub micro gram concentration and the available methods of assay were capable of measuring fractions of a milligram at best

Despite this absence of any precise tool with which to detect digitalis glycosides in the tissues or body fluids of either the pa tient or experimental animal certain precepts were entertained concerning the absorption localization and excretion of a digi talis glycoside in the human subject Perhaps it would be of interest to review these beliefs prior to any description of the data obtained by recent quantitative micrometric methods of assay

First almost all clinicians had believed that both digitalis and digitoxin were absorbed almost completely from the gastroin testinal tract This belief which probably antedated the experi mental findings of Ogawa [1] Rothlin and Travell and Gold [3] nevertheless received a certain degree of experimental proof from these latter studies

Secondly the belief was widespread that a selective concen tration of digitalis or digitoxin occurred in the heart after their administration Perhaps the major reason for this belief was a simple one namely that the dynamics of this particular organ appeared to be most radically influenced by the administration

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of a digitalis preparation There was however no unequivocal experimental verification for this belief While it is true that Rothlin[4] and Weese[5] concluded that isolated cardiac tissue removed more digitoxin from a perfusion fluid than other tissues they did not actually analyze their hearts for their digitoxin content Then too the delicacy and the precision of their method of assay were open to serious question Hatcher and Eggelston[6] moreover were unable to find digitoxin in any organ of the rat except its liver

Thirdly most clinicians believed that extravascular fluid (particularly in edematous patients) probably contained significant amounts of a digitalis preparation after its administration Here again actual experimental proof of this was exceedingly tenous[7,8] and it would appear that the real basis for this clinical belief was primarily due to the appearance of various toxic manifestations sometimes observed concomitantly with the apparent reabsorption *of an extravascular accumulation of fluid and its consequent* exit via the kidney

Fourthly the majority of clinicians again despite the contrary findings of Hatcher[9] in the experimental animal believed that the major portion of an administered digitalis glycoside was excreted in the patient s urine

Fifthly it was generally believed for many generations that man excretes or otherwise rids himself of approximately 0 1 gram *of digitalis or 0 1 mg of digitoxin a day* As a corollary of this clinical assumption it was generally believed that a patient completely digitalized with digitalis or digitoxin would completely lose all of his digitals approximately fourteen days after cessation of its administration

These five beliefs concerning the fate and disposition of digitalis or digitoxin then were those generally held by clinicians in that period of time extending from the introduction of the digitalis *leaf in 1785 by Withering*[10] *up to the last decade* at which time two extremely sensitive methods were introduced for digitoxin assay Later in this article these clinically held views will be reviewed again in the light of data recently obtained by these methods

I METHOD OF QUANTITATIVE ASSAY FOR DIGITOXIN IN BIOLOGICAL TISSUES AND FLUIDS

Although various assay methods for digitalis detection have been attempted during the past fifty years it would appear that at the present time the two most successful have been the radio isotope method of Geiling *et al* [11] and the embryonic duck heart method of Friedman and Bine [1]

The comparative merits of both methods have been discussed previously [13] and the interested reader is referred thereto Suffice it to say here that both methods are capable of detecting fractions of a microgram of digitoxin in various media and that both methods depend upon the *meticulous chemical extraction* of very minute amounts of digitoxin from the biological sample It is the difficulty of this quantitative isolation of the drug prior to its measurement by Geiger counter or embryonic duck heart preparation that may lead to errors by either type of assay In our opinion also this preliminary extraction of biological samples and later precipitation with digitonide does not allow the investigator any absolute confidence that the digitonide precipitate is unchanged cardioactive digitoxin unless it proves to be so on biological assay Only the embryonic duck heart method allows this last type of identification a fact which makes us prefer its employment Below a description of the embryonic duck heart method is detailed

Description of the Embryonic Duck Heart Assay

The method is essentially similar to that described by Paff [14] for the embryonic chick heart In our hands the embryonic chick heart assay proved to be unreliable although I suspect that our failure with this method was due to our inability to obtain fertile eggs from a single source

The fertile duck egg (White Peking China strain) is incubated for about 90 hours at 39 C The shell is partially removed the total embryo is removed and placed in a slide well containing Tyrode s solution Under a dissecting microscope the heart is removed with dissecting cataract knives and placed with four other similarly removed hearts in a second slide well containing 0 1 ml of the solution to be tested This second slide rests on the

stage of a compound microscope which is in a box automatically maintained at approximately 35 C

After the five hearts have been transferred to the second slide each is observed through the microscope and the (1) strength and rate of contraction (2) time of occurrence of an arrhythmia (usually partial or complete A V block) and (3) duration of beating are noted The occurrence of an arrhythmia or marked slowing or abrupt cessation of beating will invariably occur if 0 025 micrograms or more of digitoxin per ml of fluid is present Moreover the more digitoxin present the more rapid will this digitalis effect occur Thus five hearts immersed in 0 025 mcg of digitoxin per ml usually exhibit an effect in an average of about forty minutes whereas five hearts immersed in 0 10 mcg of digitoxin per ml exhibit an effect in twelve minutes Accordingly standards containing varying quantities of digitoxin (0 025 0 05 0 075 0 10 mcg etc) are made up and the average time for digitalis effect can be determined After these standards have been set up a series of five or more hearts are placed in the unknown sample to be assayed and the latter s content of digitoxin determined by the time taken for the hearts to exhibit the typical digitalis effect

Before digitoxin in tissue or fluid can be assayed in such manner it must be extracted from the biological sample Thus when in tissue it is removed first by repeated alcoholic extraction of the ground up tissue evaporation of the final alcoholic extract and chloroform extraction of the latter The chloroform extract in turn is evaporated and the residue dissolved in Tyrode s solution This latter solution is then tested for its digitoxin content by the immersion of the beating embryonic duck hearts within it Extravascular fluid bile and urine except for a few variations are treated in essentially the same manner

Because of the impossibility of extracting all of the minute amounts of digitoxin either in tissues or fluid it has been our custom to add known amounts of digitoxin to aliquots of tissue or fluid then perform the extraction and determine the average time for occurrence of digitalis effect in a number of hearts exposed to extractions of tissues containing initially known various amounts of digitoxin Such extractions furnish the standards for

the assay of tissue or fluids containing unknown amounts of digitoxin

The above gives a brief description of the techniques employed but if the reader should contemplate performing this method of assay he is advised to consult the specific articles[15] [16] describing these processes If proper attention is paid to the chemical measures involved this method offers a reasonably accurate tool for the study of digitoxin (or Lanatoside C) in the animal and human body Certainly the dissection of the embryonic heart and its observation for cardiac irregularity when exposed to digitoxin are simple procedures easily learned after a few hours of practice manipulation and observation

II THE FATE OF DIGITOXIN IN THE BODY AFTER ITS ADMINISTRATION

The data and conclusions described below unless otherwise stated have been obtained by employment of the embryonic duck heart preparation It is of interest that in general these results are similar to those obtained by the radioisotope technique a fact suggesting the accuracy of both methods

A The Absorption of Digitoxin

Digitoxin indeed as suspected by the clinician appears to be completely absorbed from the gastrointestinal tract As Table I demonstrates the amount of digitoxin found in the urine of normal subjects after oral administration is about the same as that found in the urine of subjects given the same amount of digitoxin by intravenous route The equivalence of these two values of course suggests that the amount of digitoxin absorbed after oral ingestion was the same as that obtained after parenteral injection

If this urinary excretion of digitoxin is used as the indicator then even the patient suffering from left ventricular failure was found to absorb the entirety of an oral dose of digitoxin[17]

B The Disappearance of Digitoxin from Blood After Parenteral Administration

We have never observed a measurable amount of digitoxin (i e 0 05 mcg /cc of serum or more) in the blood after the oral

TABLE I

THE RENAL EXCRETION OF DIGITOXIN IN YOUNG ADULTS AFTER a) ORAL AND b) INTRAVENOUS ADMINISTRATION OF DIGITOXIN (1 2 MG)

Subject	*Age*	*Weight (kg)*	*Urinary Digitoxin (Mcg)* Day 1	Day 2	Day 3	Total (3 Days)
		A Subjects Given Digitoxin Orally				
M F	39	73	44	60	85	189
S B	31	73	86	68	38	192
R B	34	86	52	28	20	100
S K	30	74	51	30	—	—
F M	35	73	60	60	19	139
Average	34	76	58	49	40	155
		B Subjects Given Digitoxin Intravenously				
R H	39	80	69	72	54	195
W W	41	80	20	50	33	103
M S	34	52	46	26	30	102
V S	46	50	50	30	78	158
Average	40	66	46	45	49	150

ingestion of digitoxin even if hugh quantities are taken Several years ago we examined the blood of a patient who had taken ten grams of digitalis with suicidal intent but no detectable amount of digitoxin was observed in his blood

When 1 2 mg of digitoxin is given intravenously approximately 50% of it disappears almost immediately from the blood stream [18] The remainder however possibly because of its adsorption by plasma albumin [19] very slowly disappears from blood over a period of two to three hours Okita *et al* [20] however found a more rapid rate of disappearance Lanatoside C given in the same dosage disappears much more rapidly (probably because it is not absorbed by albumin) so that in less than thirty minutes after its administration none could be found in the blood [15] I believe this difference between the rates of disappearance of the two respective drugs carries therapeutic significance because if rapidity of digitalis effect is desired certainly Lanatoside C with its quick departure from blood should prove the more rapidly acting drug

C Deposition of Digitoxin in Various Tissues

The long held clinical belief that a selective concentration of

digitoxin occurred in the heart does not appear to be true if either our measurements[2,1] or those of Fischer Sjoerdsma and Johnson using the radioisotope technique are valid

The results of both studies indicated that immediately following the parenteral administration of digitoxin in the rat the liver contained the greatest amount of digitoxin The heart moreover contained about the same amount of the glycoside as the kidney and lung although about five times as much as skeletal muscle Three hours after injection the quantity of digitoxin in the heart decreased approximately 80% being only slightly greater than that found in muscle and only one fifth of that still found in the liver Some time between twelve and sixteen hours no digitoxin could be found in any organ except the brain This organ apparently took up digitoxin much more slowly than other organs but retained it much longer Indeed even after twenty four hours a slight trace of digitoxin could still be detected in the brain

Essentially similar results were observed when the organs of the rabbit and dog were studied except that the kidney of the latter was found to contain the greatest quantity of digitoxin as the duration of the experiment lengthened This relative localization of digitoxin in the kidney of the dog is interesting in view of *the fact that little or no digitoxin can be found in the urine of* this species

These results of course suggest that the effect of digitalis glycosides upon cardiac dynamics is due to some specific response of cardiac musculature and this type of musculature alone to these substances There certainly seems to be little support offered by these studies to the concept that some general effect of digitalis glycosides upon all types of muscular contraction becomes primarily a cardio specific one because of a selective concentration of these substances in the heart

By means of centrifugal separation of cellular fractions of the heart (of an animal given digitoxin) and assay of their digitoxin content our studies[3] strongly suggest that neither the nuclear nor the mitochondrial fraction of the cardiac contracting cell contains significant amounts of digitoxin On the other hand the highly soluble portion of the cellular cytoplasm contains the major portion of the intracellularly deposited digitoxin

When it is remembered (1) that this same cellular fraction also contains the contractile proteins actin and myosin and (2) digitoxin appears to have no effect upon the chemical energy forming reactions of contracting muscle[13] then it seems a reason able possibility to consider that digitoxin exerts its therapeutic effect by aiding the mechanical efficiency of the contractile units Whether this last effect is mediated by cation changes initiated by digitoxin remains to be determined

D Possible Deposition of Digitoxin in Extravascular Fluid

Here again the frequently held view that considerable amounts of digitoxin may accumulate in the extravascular fluid could not be verified by our recent study In this study the extravascular fluids of the peritoneal of the pleural cavities and of the subcutaneous tissues of both cardiac and non cardiac pa tients given digitoxin over a long period of time were found to contain almost insignificant amounts of digitoxin (less than 20 mcg of digitoxin per liter of extravascular fluid) It therefore seems probable that whatever toxic manifestations a patient may suffer from or exhibit during reabsorption of extravascular fluids (with subsequent diuresis) they do not stem from any flooding of the blood and other tissues with digitoxin previously retained in edema fluid It is far more probable that the sudden shifts in cation concentration (particularly potassium) in various organs associated with reabsorption and diuresis of excess fluid are prob ably responsible for these toxic manifestations

III THE EXCRETION OF DIGITOXIN

A The Renal Excretion of Digitoxin

1 *Normal Subjects* Man seemingly differs markedly from the rat rabbit and dog in his renal handling of digitoxin The animals cited apparently are capable of excreting only a very small fraction of a given dose of digitoxin in their urine Con cerning this point there is complete agreement between investi gators employing the radioisotope technique and those[4,5] using the embryonic duck heart method

A young man on the other hand is capable of ridding himself of approximately 40 to 50% of a single dose of digitoxin However

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former rarely excretes more than two and sometimes less than 1% of the total dose[16] The reason for this difference has not been determined but it seems plausible that the reduction in rate of glomerular filtration in the old person may be responsible

If a normal individual is digitalized (e g given 1 2 mg of digitoxin in twenty four hours) and then maintained on a daily dose of 0 1 mg the renal excretion of digitoxin differs (see Figure 1) from that observed in the person given just a single dose of 1 2 mg The renal excretion of the subject given the maintenance dose will not progressively fall after the third day as noted above but will level off so that he will excrete fairly consistently and indefinitely 32-44 mcgs of digitoxin a day that is about 32 44% of the maintenance dose

This daily excretion rate of 32-44 mcgs of digitoxin in a subject being maintained on the drug seems to be characteristic and indicative of a satisfactory state of complete digitalization When considerably more digitoxin is excreted daily the danger of overdosage is imminent We have found[16] that when 80 or more mcgs of digitoxin are excreted daily in a chronically digitalized subject symptoms and signs of overdosage invariably will soon appear

2 *Cardiac Patients* Patients suffering from acute left ventricular failure excrete digitoxin just as readily as do normal subjects[6] suggesting also as mentioned above that absorption is unimpaired On the other hand patients suffering from right ventricular failure are capable of excreting only about half of the usual amount of digitoxin found in the urine during the first twenty four hours following initial digitalization This reduction in renal excretion is not due to a possible inhibition in the absorption of digitoxin because it also was observed in patients who received their digitoxin parenterally Apparently then the decrease is due to an interference with renal circulation Certainly with improvement in the state of congestive failure the renal excretion of digitoxin rapidly rises to the usual level This return to the normal rate may indeed usually does occur some time between the second and third days post digitalization

The compensated cardiac patient who has been digitalized and then maintained on a daily dose of 0 10 to 0 15 mg of digi

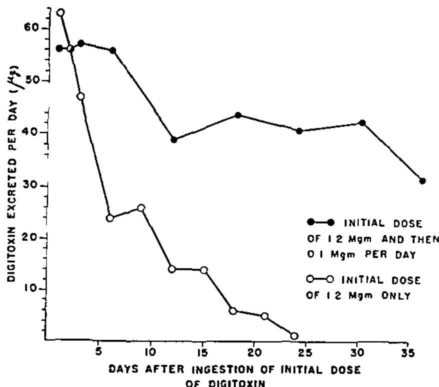


Figure 1 The renal excretion of digitoxin in normal human subjects after (1) A single initial dose of digitoxin and (2) initial dose followed by daily ingestion of digitoxin Reproduced from *Circulation* 2 753 1950 by permission of Grune and Stratton Inc

(see Figure 1) it usually takes him two or more weeks to do so Thus during the first three days after the administration of digitoxin the normal subject will excrete only 3 to 5% per day of the total dose given regardless of the amount given If only 100 mcg are given for example the renal excretion during the first twenty four hours will be about five mcgs but if 1200 mcgs are given about 60 *mcgs (i e 5% of the total dose)* will be excreted After the third day the percentile excretion decreases so that at the end of six days about 2% of the total amount initially given is excreted daily

The older person (i e over sixty years of age) excretes digitoxin much less readily than the young adult Whereas the latter excretes 3 to 5% of the total dose the first twenty four hours the

of digitoxin in their bile is rather surprising in view of the initial selective localization of administered digitoxin in the liver Apparently this storage is temporary and not a prelude either to the immediate destruction or excretion of digitoxin

Our findings in the experimental animal were confirmed in a later study of the digitoxin content of human bile Such bile after the administration of 1 2 mg of digitoxin was found to contain too small a quantity of digitoxin to be detected by our method However if as much as 20% of the administered digitoxin had been excreted in the bile it would have been detected by us It would seem therefore that although man s kidney handles digitoxin differently than that of the common laboratory animals his liver does not do so

C Intestinal Excretion of Digitoxin

Considerable confusion exists about the intestinal excretion of digitoxin Geiling [7] and Fischer *et al* [2] examining the feces of dogs cats and rats observed that in these species somewhere between 10 and 25% of a given dose of digitoxin is excreted as *unchanged* digitoxin in the feces and about twice this amount as digitoxin metabolites On the other hand studies made with the embryonic duck heart method indicate that although the rat does excrete about ten to fifteen per cent of a given dose of digitoxin in its feces this digitoxin is derived from the bile and not the intestinal wall

The disagreement between the results obtained may well be due to the fact that the embryonic duck heart will assay only digitoxin when it is intact in respect to its cardioactive properties whereas the digitoxin substance isolated by the Geiling group is actually a digitonide precipitate which may or may not represent intact digitoxin as discussed earlier The conflict however is at best of academic interest with no real relevance to the important pharmacological aspects of digitoxin It is important however *to point out that the degree of radioactivity alone of a biological* sample after the administration of radioactive digitoxin cannot be employed as a measure of digitoxin itself It may easily be radioactive fragments of the original steroid skeleton of the drug

toxin excretes approximately the same amount of digitoxin as the normal subject Eighteen such patients studied by us [6] were found to excrete approximately 41 mcgs of digitoxin a day after an average period of twenty four months of adequate digitalization Overdosage in these patients also was reflected by a daily renal excretion of eighty or more mcgs of digitoxin

B The Hepatic Excretion of Digitoxin

If the preceding data concerning the duration of urinary excretion of digitoxin after a single dose is correct then it hardly seems likely that much digitoxin is excreted by the liver into bile Because if such excretion were a major or efficient one it seems hard to believe that the human subject takes two or more weeks to excrete or rid himself of a single dose of 1 2 mg It is of course possible that the drug may be tenaciously held by various tissues and thus available in only minuscule amounts for excretion at any given instant

The answer to this question of course can only be obtained by direct measurement of the drug in the bile of the animal or of man This of course was not possible until very recently although Hatcher and Eggelston [6] believed that their detection of some digitoxin in the urine of a rat after biliary obstruction suggested that at least some digitoxin was excreted in the bile Geiling [7] employing the radioisotope method was the first to analyze the bile itself in the experimental animal (dog) He found about 11% of the total amount of radioactivity administered originally as digitoxin in the bile collected for forty eight hours

Employing the embryonic duck heart method we found that the bile of the rat dog and rabbit did contain digitoxin but it never accounted for more than 10% of the digitoxin administered It is possible of course that some of the glycoside could have been altered in its passage through the bile passage thus not exerting a cardioactive effect upon our duck hearts However this seems unlikely because in Geiling s analysis as mentioned above only 11% of the total radioactivity administered was detected in the bile

The failure of the rat and rabbit to excrete greater quantities

ized person if 200 or more micrograms are given daily then no more than 100 of this could be excreted However the remaining 100 mcgs twice exceeds the maximum capacity of destruction (i e 50 micrograms a day) leading to a toxic accumulation This is the probable reason why so much toxicity was encountered clinically when a dose of 0.2 mg was advocated as a proper maintenance dose by some investigators

V A COMPARISON OF THE PREVIOUSLY HELD CLINICAL VIEWS AND RECENTLY OBTAINED EXPERIMENTAL DATA CONCERNING THE FATE AND DISPOSITION OF DIGITALIS AND ITS GLYCOSIDES

At the beginning of this section I listed five clinical views about the disposition of digitalis glycosides in the animal body It might be of interest now to review these in the light of new but not necessarily absolutely correct experimental data

First the clinical view that digitalis and digitoxin are completely absorbed has been borne out by all experimental studies Secondly the experimental data verifies the clinical view about the time taken for digitalis and digitoxin to disappear in man Thirdly the experimental data partially but not completely supports the idea that man excretes a major portion of ingested digitoxin in his urine However experimental data appears to refute the idea that a digitalis glycoside (1) is selectively concentrated in cardiac tissue or (2) is stored in significant amount in extravascular fluids

VI THE ULTIMATE GOAL IN THE PHARMACOLOGICAL STUDY OF DIGITALIS AND ITS GLYCOSIDES

All of the data obtained during the last decade about the fate and disposition of digitoxin interesting and perhaps even instructive as it may be still does not allow the student of digitalis therapy to approach any closer to the real core of his enquiry Such a student actually and indeed understandingly wants to know above all else Precisely (i e chemically or physico chemically) how does digitalis or its glycosides restore the failing musculature of the heart to a near normal state?

Neither the assay nor the catheterization techniques have

IV THE DESTRUCTION OF DIGITOXIN WITHIN THE BODY

Although it seems very probable that both the experimental animal and man destroy some digitoxin the actual evidence available allows no absolute certainty about such a process In deed various types of tissue when tested in *in vitro* studies appear strangely incapable of either hydrolyzing or otherwise destroying digitoxin [8 29] Actually we assume that a consider able portion of digitoxin is destroyed in the experimental animal primarily because we cannot recover a sufficient fraction of any administered amount in the various excretions of the animal to account for its rapid disappearance from both the tissues and fluids of the same animal This evidence of course is primarily negative but it nevertheless is strong evidence for the assumption that some digitoxin must be destroyed in the animal body

In man objective data about this point is almost completely lacking and even following the recent introduction of the more sensitive methods of assay it still remains quite uncertain whether or not digitoxin is destroyed in man If however our present methods of assay are correctly estimating the total amount of digitoxin excreted via urine and feces then almost half of a daily maintenance dose of 0 10 mg is disappearing in some fashion other than by excretion Also the apparent appearance of digi toxin metabolites in urine after the administration of radio active digitoxin suggests that some deterioration of this steroid must take place in the human body

If such destruction actually occurs however it is certainly placed at a snail s speed because were there a rapid process in volving a considerable portion of the body s total digitoxin it is extremely doubtful that the normal subject would continue to excrete a relatively fixed but minute amount of digitoxin for days and days after a single administration of only 1 2 mg Indeed any body process capable of destroying at most a scant 50 75 micrograms of digitoxin a day must be considered as one of phy siologically insignificant proportions

This minute capacity of man to destroy digitoxin explains his extreme susceptibility to overdosage Thus although about 30 to 50% of a given maintenance dose may be excreted by the digital

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furnished even a reasonably solid clue to this terribly important enigma Mere quantitative reconnoitering of the digitalis path ways in the body of course cannot be expected to do so Mere quantitative descriptions of cardiac output before, during and after digitalis administration also cannot be expected to furnish an answer either Actually upon reflection, it is obvious that cardiac output is not just a function of cardiac *contractility* but a resultant of this last *plus* arteriolar changes in resistance Thus even if force of cardiac thrust were halved if this were instantaneously accompanied by reflex arteriolar vasodilatation the cardiac output might continue unchanged This last is sometimes forgotten in the welter of catheter obtained statistics

There is needed then a new set of tools that will allow the investigator to explore the interior of a single cardiac cell to measure the physico chemical reactions of the contractile proteins and of the various ions in the milieu surrounding these protein entities both before and after the administration of digitalis In other words the further possibly lucrative study of digitalis lies not in a study of the steroid itself but in those cellular substances whose behaviour has been altered by their contact with digitalis

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Selected Studies on the Metabolic Fate of Radioactive Digitoxin in Man

GEORGE T OKITA*

OVER ONE AND ONE HALF centuries have elapsed since Withering first noticed the cardiac action of digitalis[1] Since then there has accumulated a voluminous literature on the clinical and pharma cological effects of the digitalis glycosides However to date knowledge concerning the metabolic fate of digitalis in human subjects is very limited The reason for this general lack of knowl edge can be attributed to the fact that only minute amounts of the drug are required to produce the cardiotonic effects This therefore makes it extremely difficult to measure microgram quantities or less of the drug in body tissues It has only been within recent years that new methods have been devised which enable one to quantitatively assay sub microgram amounts of digitalis

Three of the more sensitive methods are the radioisotope method of Geiling *et al*[2] the polarographic method of Hilton[3] and the embryonic duck heart bioassay method of Friedman and Bine[4] By utilizing these sensitive methods it has been possible to obtain information on the blood level tissue distribution and excretion of digitalis in human subjects[5-14] For an excellent re view of the behavior and fate of digitoxin in experimental ani mal and man one can refer to a recent article by Friedman St George and Bine[15]

It is the purpose of this review to summarize our findings on the study of the metabolic fate of digitoxin in human subjects using the radioactive isotope tracer technique

USE OF RADIOACTIVE C 14 DIGITOXIN

The extreme sensitivity the accuracy and the relative sim plicity of the radioactive technique are some of the attractive

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digitalis plants were administered C 14 carbon dioxide at frequent intervals After each administration of the radioactive gas the carbon 14 in the chamber atmosphere was monitored by using an end window Geiger counter For maximum growth artificial illumination was provided immediately above the plant chamber After the four to six weeks growing period there was an eight to ten fold increase in leaf surface The leaves were then harvested and dried at room temperature before subjecting the leaves to the extraction procedure for the isolation of the cardiotonic principle

Essentially the extraction of the radioactive digitoxin from the dried plants was accomplished by solvent solvent extraction followed by chromatographic fractionation using ion exchange and adsorption chromatography columns The isolated radioactive digitoxin was then further purified by repeated recrystallizations from aqueous ethanol From 20 grams of the dried plant material, approximately 5 mg of radioactive digitoxin were obtained Depending upon the amount of carbon 14 administered to each *Digitalis purpurea L* plant the specific activity of the labeled drug varied from 0 26 to 0 54 uc per milligram

Purity and identification of the radioactive drug was tested by a number of methods [16] Melting point determination crystallographic examination polarographic analysis color reaction tests and paper chromatography of the labeled compound all confirmed that the isolated drug was radioactive digitoxin

B Extraction and Assay of C 14 Digitoxin from Biological Samples

A detailed account has also been presented earlier for the isolation of unchanged digitoxin from tissues and body fluids [1, 13, 14] From biological samples such as blood and solid tissues an initial solvent extraction was effected using either hot methanol or 80% ethanol plus chloroform to liberate the protein bound digitoxin For urine samples an initial solvent extraction was effected using 50% ethanol In all cases approximately 2 mg of non labeled digitoxin was added as carrier to the extraction mixture to aid in the isolation of the labeled glycoside A combination of appropriate solvent solvent extractions plus chromatographic sep

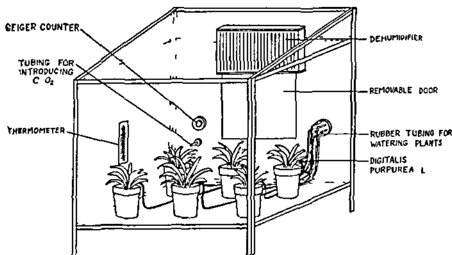


Figure 1 A plant growing chamber used for the biosynthetic labeling of medicinal plants with radioactive carbon dioxide Figures 1 9 reproduced from *J Pharm Exp Thera* (*110* 244 1954 *113* 376 1955 *115* 371 1935) by Okita *et al* Courtesy the Williams & Wilkins Company

features of this method Using radioactive digitoxin it is possible to isolate and detect as little as 0 02 microgram of the labeled drug from a biological sample provided non labeled digitoxin is added to the sample as carrier to aid in the isolation of micro amounts of the drug Another advantage of the isotope method is that by using biosynthetically labeled drugs one can follow not only the unchanged drug but also its metabolic products since the compound is uniformly labeled As a result various frac tions from the parent compound can be conveniently traced and accounted for

A Biosynthesis and Isolation of C 14 Digitoxin

The radioactive drug administered to the patients was pre pared by biosynthesis using *Digitalis purpurea L* plants exposed to an atmosphere of carbon 14 dioxide A detailed account of the method of biosynthesis and isolation of the crystalline labeled glycoside has been reported earlier [16] Briefly the method involves the placement of several *Digitalis purpurea L* plants in an air tight plant growing chamber similar to the one shown in Figure 1 During the four to six weeks growing period in the chamber the

heart method of assay Friedman and co workers[8] were able to follow the disappearance rate of digitoxin from blood of four normal subjects up to three hours after its parenteral administration This same group also reported that lanatoside C was removed from the blood stream of ten human subjects within thirty minutes after its intravenous injection[5] Hilton[11] using the polarographic method reported that digitoxin was eliminated from the blood stream within three to five hours after its injection

Using the radioisotope method we have investigated the rate of disappearance of unchanged digitoxin and its conversion products from the blood stream of eight cardiac patients who received a single intravenous dose of the labeled glycoside[13] The eight patients with congestive heart failure were divided into two equal groups one group receiving 0 5 mg of radioactive digitoxin and the other group receiving from 1 2 to 1 5 mg Prior to the administration of the radioactive drug digitalis preparations were withheld for fourteen to thirty four days in order to permit the administration of a relatively large dose of digitoxin Since urine samples were also collected for a renal excretion study further digitalis therapy was discontinued for fourteen days or longer after administration of the labeled drug Ten to 20 ml blood samples were withdrawn by venipuncture at various time intervals between immediate to ninety six hours after injection of the drug After withdrawal of each blood sample the blood was quickly transferred into a heparinized glass stoppered tube and immediately stored at −17 C

A Concentration and Persistence of Drug in Blood

Figure 2 shows a graphical representation of the blood level curves of unchanged digitoxin and total C 14 for two different doses of the labeled glycoside on the basis of the per cent of the administered dose remaining in the vascular system Figure 3 shows the blood level curves for the two doses when the concentration is expressed in terms of microgm or microgm equivalent per 100 ml of blood It can be seen from the curves that within one hour after injection of the labeled drug there is a rapid initial decline in the concentration of the drug followed by a gradual leveling off of the curve Within two minutes after

aration were utilized to isolate the unchanged drug from the biological sample All the radioactivity in the various fractions other than that of the unchanged drug were combined and considered to represent radioactivity from metabolic products of the parent compound

Determinations of radioactivity of the various extracted fractions except the original tissue residue from the homogenate fraction were made using an internal gas flow Geiger counter The tissue residue was combusted to carbon dioxide in a vacuum combustion line and counted in an ionization chamber using a vibrating reed electrometer according to the method of Brownell and Luckhardt[17] All counting equipment was calibrated against a C 14 standard obtained from the National Bureau of Standards All radioactivity measurements were performed by counting for periods long enough to give a standard error of less than plus or minus 5% Using a known amount of radioactive digitoxin as a control and subjecting it to the extraction procedure described recoveries of ninety six plus or minus 5% were obtained The term microgm equivalent is used to express the amount of the original drug converted into metabolic products that is if one microgm of radioactive digitoxin has a certain number of disintegrations per minute then the conversion products having the same number of disintegrations per minute are considered to represent one microgm equivalent

Due to the minute amount of unchanged digitoxin recovered from biological samples conventional physical identification and characterization tests could not be employed on the compound However various tests described in an earlier publication[1] such as comparison of Rf values of the isolated drug with non radioactive standard digitoxin by paper chromatography color reaction tests and the use of the isotope dilution method for determining the constant specific activity of a compound confirmed the presence of only unaltered digitoxin

BLOOD LEVEL STUDIES

It has only been within the past decade that quantitative information has been obtained on the blood level of digitoxin in human subjects Recently using the sensitive embryonic duck

used. A similar comparison of the blood curves on the basis of the amount of glycoside per 100 ml. of blood indicates that the concentration is dose dependent. However, from the two dosage ranges used it is not possible to determine whether this relationship is proportional.

B. Disappearance Rate from Blood

A semi-logarithmic plot of the disappearance curve of unchanged digitoxin in blood is shown in Figure 4. If we assume that this plot is the resultant of first order or quasi first order reactions, the curve can be resolved into two straight line components.[18, 19] Corresponding regression coefficients (k), half times ($t_{1/2}$) and turnover times (t_t) may be calculated from the slope of these lines. The fastest component of the curve is represented by a biological half time of fifteen to thirty minutes with a turnover time ($t_{1/2}$ x 1.45) of twenty-three to forty-five minutes. The biological half life of the second component is forty-eight to fifty-four hours with a turnover time of approximately seventy-two to

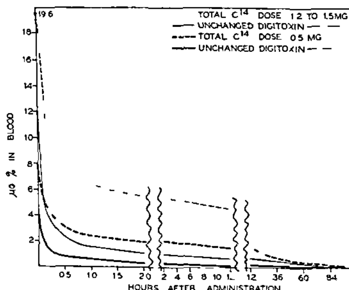


Figure 3. Blood level curves showing microgram per cent of unchanged digitoxin and total C^{14} in blood after single intravenous administration of radioactive digitoxin.

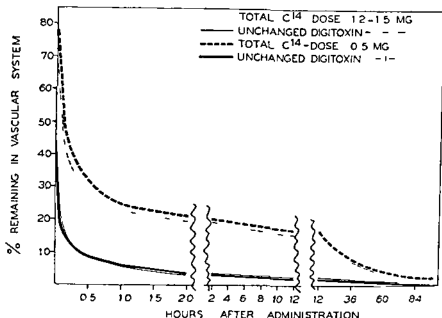


Figure 2 Blood level curves showing per cent of dose remaining in vascular system as unchanged digitoxin and total C[14] after a single intra venous administration of radioactive digitoxin

administration of the drug approximately 42% of the injected dose can be detected in the circulating blood as unchanged digi toxin At the end of fifteen minutes there is approximately 12% after one hour 6% six hours 3% twenty four hours 2% and after ninety six hours less than 1% Since renal excretion studies indi cate that digitoxin can be detected in the urine up to twenty three to fifty days after its administration it is very likely that digitoxin is present in the blood as long as it is being eliminated into the urine

The maximum amount of unchanged digitoxin found in the blood was between 4 to 12 microgram per 100 ml of blood This concentration was observed within two minutes after injection of 0 5 to 1 5 mg of C[14] digitoxin Within one hour after administra tion the blood level fell below 2 microgram per cent

Comparison of the blood level curves on the basis of the per cent of the injected dose remaining in the circulating blood indi cates that there is no appreciable difference between the dosages

TISSUE DISTRIBUTION OF DIGITOXIN

Considering the very specific effect of digitoxin upon the heart many of the earlier investigators postulated that the cardiac drug had a selective affinity for the myocardial tissue. However until recently there has been no direct evidence to substantiate this assumption. In experiments with various laboratory animals Geiling *et al.* [0] and Fischer *et al.* [1] using the radioisotope technique and Friedman *et al.* using the embryonic duck heart method of assay found that digitoxin had no selective affinity for the cardiac tissue of any of the animals studied. The liver, kidney and gastrointestinal tract were found to have higher concentrations of the drug than the heart. In human subjects we have found a somewhat similar type of distribution using C^{14} digitoxin.[14]

A. A Method of Study in Human Subjects

Three terminal patients were selected for this study. A summary of the pertinent clinical data is presented in Table I. During the terminal stages multiple doses of radioactive digitoxin

TABLE I

CLINICAL DATA ON TERMINAL PATIENT

Patient	*Sex*	*Age*	*Weight (Kgm.)*	*Diagnosis and Cause of Death*	*Intravenous C^{14}-Digitoxin*		*Interval Between Last Dose and Death*
					Mgm.	*Days Before Death*	
E. W.	F	74	40	Severe generalized atherosclerosis. Death due to cerebral vascular thrombosis	0.2 0.1	5 2	16 hrs.
M. S.	M	66	87	Acute myocardial infarction, auricular flutter, uremia. Death due to uremia	0.1 0.1 0.1 0.1 0.1 0.1	11 10 6 5 4 2	36 hrs.
T. K.	F	60	47	Hepatic carcinoma, metastatic. Death due to carcinoma to is	0.5 0.1 0.1 0.1 0.1 0.1	6 5 4 3 2 1	35 hrs.

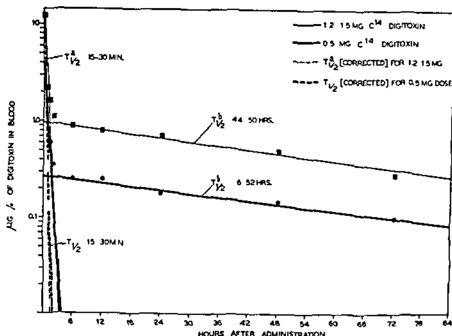


Figure 4 Semi logarithmic plot showing disappearance rate of unchanged digitoxin in blood after intravenous administration of C^{14} digitoxin

eighty one hours Comparison of the biological half life of digitoxin between the two dosages studied suggests that the rate of disappearance of the unchanged drug is not dose dependent

Although no definitive statement can be made concerning the significance of the two rate components it might be assumed that the rapid rate of $t_{½a}$ = 15 to 30 minutes may represent the rate at which digitoxin in the blood is equilibrating with the various body tissues The slower rate of $t_{½b}$ = 48 to 54 hours may represent the rate at which the loosely bound glycoside is being liberated from the body tissues It is believed that there is at least another major component representing the more "firmly bound glycosides with a still slower rate which may be detected if the blood concentration was followed for a longer period As will be mentioned later renal excretion studies indicate that this third component has a biological half life of approximately nine days with a turnover time of thirteen days

B Concentration of Unchanged Digitoxin and Its Metabolites in Tissues

The concentration of unchanged digitoxin and its metabolic products in the organs of the three patients are summarized in graphical form in Figure 5 and expressed on a tissue weight basis It can be seen from Figure 5 that as in experimental animals the myocardium in all three terminal patients had no greater selectivity for the cardiac glycoside than did the other organs On a tissue weight basis the kidney and contents of the gall bladder jejunum ileum and colon had a higher concentration of the unchanged drug than did the cardiac tissue

Although there is no selective affinity of the drug for the myocardium one is impressed by the minute amount of digitoxin (approximately 2 microgram or less per 100 gm of tissue) required for the cardiotonic action of digitoxin Considering the minute amount of drug required and the steroid configuration of the cardiac glycosides one is tempted to postulate that in cardiac failure digitalis may act as a substitute for a naturally occurring cardiotonic steroid hormone

The site with the highest concentration of unchanged digitoxin was the colonic content which had from 4 6 to 13 0 microgram per cent This was followed by the gallbladder contents the jejunal contents and the kidney with 1 2 to 3 7 microgm per cent and the ileal contents lung liver jejunum ventricle auricle adrenal and spleen with 0 6 to 1 9 microgm per cent The high concentration noted in the colonic content is believed to reflect the concentration of substances through reabsorption of water by the colonic mucosa The concentration in the blood was very low in comparison with the organs mentioned while only trace or no detectable amount was found in skeletal muscle

It is worthy of note that in almost all organs studied there was a higher concentration of metabolic products than the unchanged drug The site with the highest concentration of metabolic products were the gallbladder contents the jejunal contents and the spleen with from 10 0 to 21 0 microgm equivalent per cent Moderate to high concentrations were noted in the liver gallbladder jejunum ileal contents colonic contents and

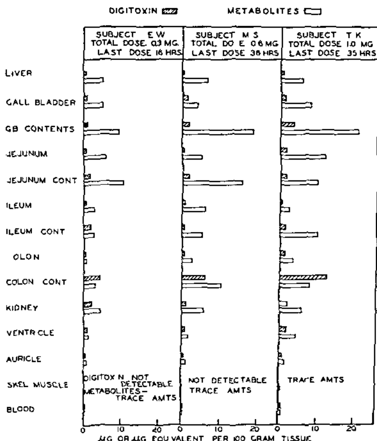


Figure 5 Tissue distribution of radioactive digitoxin in human organs Amount per 100 gm tissue

were administered intravenously at varying intervals until a short time before death Multiple doses were administered in preference to a single dose in order to maintain adequate tissue concentrations of the drug Autopsies were performed within two hours after death and tissue samples were obtained at this time Whole organs were weighed and either an aliquot or the entire organ was immediately frozen with solid carbon dioxide and stored at −17 C in order to prevent degradation of the parent compound The extraction procedure employed for the isolation of unchanged digitoxin and the fractionation of metabolic products from tissue samples has been described in the original publication [14]

tration of the drug quantitative determinations could not be performed

With respect to the metabolic products of digitoxin the liver also was found to have the largest quantity Fifteen to 23% of the administered dose was found in this organ Moderate amounts were found in the jejunum ileum kidney and blood Lower quantities were found in the other organs

D Detoxification of Digitoxin

In order to obtain information concerning the organs involved in the metabolic conversion of digitoxin the metabolite digitoxin ratio was calculated for each organ These results are presented in Table II As indicated by its high metabolite digitoxin ratio the liver is believed to be the main organ of detoxification of the cardiac glycoside The very high ratio found in the spleen is diffi cult to explain since this tissue is not considered to be an impor tant detoxifying organ However it is possible that the high ratio may be due to the accumulation of metabolite protein complexes by the reticulo-endothelial cells of the spleen

The relatively low metabolite digitoxin ratio found in the kidney ventricle auricle lung and adrenal suggests that these organs are not important detoxifying organs and play at most a minor role in the metabolic conversion of the cardiac glycoside The comparatively high ratio observed in the gallbladder con

TABLE II

METABOLITE DIGITOXIN RATIO OF VARIOUS TISSUES

Tissue	*E B*	*M S*	*T K*
Liver	8 1	12 7	6 1
Gall bladder contents	7 9	8 9	5 8
Jejunum	7 5	8 8	6 9
Jejunum contents	5 5	8 1	5 6
Ileum	6 2	8 8	7 1
Ileum contents	1 5	8 5	6 3
Colon	2 4	4 4	2 4
Colon contents	0 7	1 6	0 6
Kidney	2 0	4 8	2 5
Ventricle	1 7	2 5	2 3
Auricle	1 9	2 4	1 5
Spleen	17 2	11 2	18 9
Lung	1 8	2 2	1 6
Adrenal	3 0	2 6	1 8
Blood	5 0	3 5	3 6

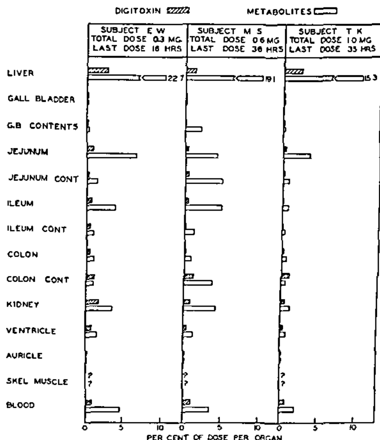


Figure 6 Tissue distribution of radioactive digitoxin in human organs Per cent of dose per organ

kidney Lower concentrations were found in the tissues of the ileum colon ventricle auricle lungs adrenal and blood

C Per Cent of the Administered Dose in Organs

The amount of the drug in terms of the per cent of the total administered dose per organ is presented in Figure 6 For the unchanged drug the liver was found to have the largest amount (1 5 to 2 8%) followed by the colon contents kidney blood ventricle jejunum jejunal contents and ileum Lesser quantities were found in the spleen colon ileal contents gallbladder contents gallbladder and auricle It is surmised that some of the glycoside is also stored in the skeletal muscle but due to the low concen

is indicated by the passage of labeled products into the small intestine via the biliary tract and their reabsorption by the intestinal mucosa Reabsorption by the intestine is shown by the lower concentration of labeled compounds in the ileum and ileal contents as compared with the jejunum and jejunal contents (see Figure 5) Worthy of note is the greater rate of reabsorption of metabolites by the small intestine as compared with the reabsorption of unchanged digitoxin This is suggested by the decrease in the metabolite digitoxin ratio during passage of the labeled products from the small to the large intestine

The present data provide no information regarding the excretion of unchanged digitoxin via the intestinal wall We are presently seeking patients with complete biliary fistulas so that fecal assays for the labeled drug can be carried out after its intravenous administration Studies with experimental animals indicate that in the rat and the dog digitoxin is excreted by the intestinal wall [0, 3]

B Renal Excretion

The first quantitative study conducted on the renal excretion of digitoxin in human subjects was reported by Friedman and co workers in 1949 [6] These investigators found that approximately 40% of a digitalizing dose (1 2 mg) is excreted over a period of twelve to twenty four days

Again using the radioisotope method we have followed the renal excretion of digitoxin and its metabolic products in the eight cardiac patients who participated in the blood level experiment Simultaneously with the blood level studies daily twenty four hour urine samples were obtained and then lyophilized by the freeze dry method The method of extraction and assay of the labeled compounds from the lyophilized urine was reported earlier [1]

1 EXCRETION GRADIENT

The average daily renal excretion rates of the labeled compounds for the four patients who received a 0 5 mg of radioactive digitoxin intravenously is shown in Figure 7 Figure 8 shows a similar plot for the four patients who received from 1 2 to 1 5 m g of the labeled glycoside As illustrated by the curves

tents and in the small intestine may reflect the passage of digi toxin and metabolites from the liver without actual degradation of the parent compound in these two organs However it is not possible to rule out metabolic conversion in the intestinal mucosa since it is possible that the ratio may not have risen significantly above the liver ratio due to intestinal reabsorption of metabolites by the small intestine proceding at a more rapid rate than for the unchanged digitoxin The moderately high rate of 3 5 to 5 observed in the blood may represent either the final ratio after mixing of labeled products released from organs having different ratios or metabolic conversion of the drug by enzymes in the blood or perhaps both

EXCRETION OF DIGITOXIN

A Biliary Excretion

The excretion of digitoxin and its metabolic products by the liver is indicated by the presence of these compounds in the gall bladder contents The amount of the unchanged drug found in the bile ranged between 1 to 4 microgm per 100 ml Assuming that the terminal patients secreted approximately 500 ml of bile per day roughly 5 to 20 microgm of digitoxin may have been excreted by the liver via the biliary route This represents be tween 1 to 2% of the administered dose Although this estimate may be low since bile samples were obtained between sixteen to thirty six hours after administration of the drug it nevertheless suggests that biliary secretion plays a minor role in the elimina tion of digitoxin

St George *et al* [10] obtained bile from two subjects who had biliary fistulae and reported that they could not detect digitoxin in the bile fluid Since their bioassay method could not detect less than 0 5 microgm of digitoxin per ml of fluid they calculated that if digitoxin were eliminated by the biliary route it must amount to less than 20% of the administered dose

The concentration of metabolites of digitoxin in the bile amounted to between 10 21 microgm per 100 ml of fluid This represents approximately 10 to 17% of administered dose when calculated on the same basis as for the unchanged drug

The entero hepatic cycling of digitoxin and its metabolites

approximately nine days and a turnover time of thirteen days for both of the dosages employed This is in good agreement with the known clinical evidence for the long cumulative action of digitoxin

2 PERSISTENCE

It can be seen from results shown in Figures 7 and 8 that the injected radioactive digitoxin is excreted over a considerable period of time Minute amounts of the unchanged drug can be detected up to twenty three to fifty days after administration of the glycoside depending upon the dosage used Metabolic products of digitoxin have been assayed in the urine up to thirty one to eighty days

3 COMPARISON BETWEEN UNCHANGED DIGITOXIN AND ITS METABOLITES

Another significant finding was the relatively small amount of unchanged digitoxin eliminated through the renal route in

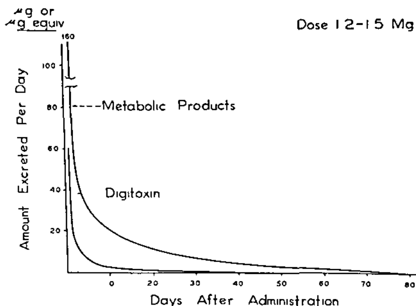


Figure 8 Average daily renal excretion rate of unchanged digitoxin and its metabolic products for four cardiac patients receiving C digitoxin Dose—1 2 to 1 5 mg I V

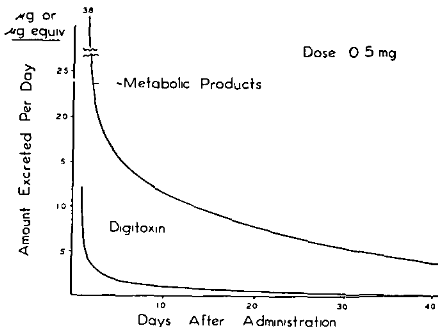


Figure 7 Average daily renal excretion rate of unchanged digitoxin and its metabolic products for four cardiac patients receiving C^{14} digitoxin Dose —0 5 mg I V

in Figures 7 and 8 there is a marked initial excretion of both digitoxin and its metabolites during the first two days after administration of the radioactive drug followed by a gradual leveling off of the excretion gradient thereafter During the initial three day period 20% of the administered dose is eliminated with about half of this amount being excreted during the first 24 hours

The average amount of unchanged digitoxin excreted in the urine during the first second fifth twelfth and twenty third day after administration of 0 5 mg of the labeled drug were 13 3 2 0 7 and 0 2 microgm respectively For the corresponding time intervals at the higher dose the amounts of digitoxin excreted were 61 14 4 3 5 and 1 microgm respectively The data therefore indicate that the amount of drug excreted daily is dependent upon the amount in the body

A semi log plot of the disappearance curve of unchanged digitoxin in urine is illustrated in Figure 9 Graphical calculation of the exponential rate constant indicates a biological half life of

metabolites may represent water soluble hydrolytic and conjugation products of digitoxin At the present time we are attempting to identify some of these metabolic products

There is also evidence which suggests that at least part of the digitoxin molecule is broken down into one carbon fragments Urea isolated from urine of patients receiving digitoxin and recrystallized a minimum of eight times was found to have a specific activity of seven to ten disintegrations per second per gram Since the carbon atom of urea is derived from the carbon dioxide pool [4] this would indicate that some of the labeled carbon atoms of digitoxin entered the carbon dioxide pool It should be pointed out that the urea was assayed by the ionization chamber vibrating reed electrometer method [17] since it could not be assayed in a windowless gas flow geiger counter due to its extremely low specific activity The metabolic products assayed by the gas flow counter are not biochemical compounds resynthesized from labeled one carbon fragments but represent direct conversion products of the parent compound The low level of C^{14} administered (less than 0 5 uc) and the great dilution in radioactivity of endogenously formed compounds arising from the labeled one carbon pool prevent the detection of these substances using a gas flow geiger counter

C Fecal Excretion

Daily fecal samples were also obtained over a period of 14 days from two of the patients who participated in the renal excretion study Approximately 9% of the original dose was excreted as unchanged digitoxin and 8% as metabolic products Since 60 to 80% of an administered dose of digitoxin is excreted by the urine in both the unchanged and metabolic form the main organ involved in the ultimate elimination of digitoxin plus its metabolic products is the kidney However if only the unchanged drug is considered the amount excreted in the urine is approximately the same as that excreted in the feces

PLACENTAL TRANSFER OF DIGITOXIN

Studies have also been conducted to investigate the passage of labeled digitoxin across the placental barrier of pregnant

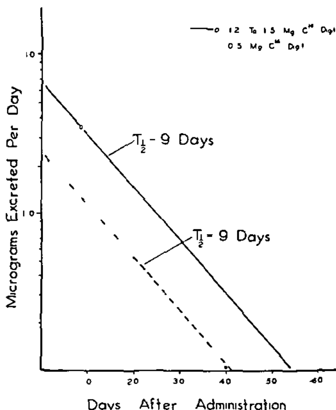


Figure 9 Semi logarithmic plot showing disappearance rate of unchanged digitoxin in urine after intravenous ad ministration of C^{14} digitoxin

comparison with the larger amount of metabolic products Ap proximately 8% of the administered glycoside was excreted in the unchanged form over a period of thirty days or longer while approximately 71% was excreted as metabolic products There fore this demonstrates that the major portion of the original drug is converted into metabolic compounds

Of the metabolic products it was found that 8 to 15% of the metabolites was excreted as choloroform soluble metabolites whereas the remainder was in the form of water soluble com pounds The significance of the chloroform soluble metabolites lies in the fact that being fat soluble they may be closely related in structure to the parent compound while the water soluble

its metabolites in the aborted fetuses In the near term fetus 0 84% appeared as the unchanged drug and 3 49% as metabolic products This difference may be attributable to the increase in size of the near term fetus since there was no significant increase in the concentration of labeled compounds on a tissue weight basis

When the total radioactivity in the maternal and in the fetal body was calculated on an equivalent body weight basis it was found that the near term fetus had almost twice the concentration of the maternal body while the eleven to twelve week fetuses had from three to six times that amount

C Distribution of Digitoxin and Its Metabolites in the Fetus

The concentration of labeled digitoxin and its metabolic products in the various organs of eleven to twelve week fetuses is shown in Figure 10 The fetal heart and kidney had relatively higher concentrations of the labeled drug and its metabolites than did the other organs that were studied In all organs there was a higher concentration of the metabolic products than there was of the parent compound The presence of metabolites in the fetal tissues suggests either a metabolic conversion of the cardiac glycoside by the fetal tissues or passage of the metabolites across the placental barrier or perhaps both The high metabolite to digitoxin ratio noted in the fetal liver may be an indication that drug detoxification is already occurring in the liver by the eleventh week of gestation The passage of digitoxin across the blood brain barrier correlates well with the known effects of digitalis on the central nervous system

The concentration of labeled compounds in the organs of the

TABLE III

AMOUNT OF C[14]-DIGITOXIN AND ITS METABOLITES IN HUMAN FETUS

Experiment	*Dose (Mg)*	*Approx Length of Gestation (Weeks)*	*Time After Injection of Drug (Hrs)*	*Per Cent of Injected Dose in Fetus*	
				Digitoxin	*Metabolites*
1	0 25	11	5 0	0 05	0 18
2	0 50	12	3 5	0 10	0 33
3	0 50	12	2 8	0 08	0 28
4	0 50	34	1 7	0 84	3 49

women and to determine the relative concentration of labeled compounds in the various fetal organs [5]

Earlier studies conducted by our group on rats and guinea pigs [6] indicate that C^{14} digitoxin crosses the placental barrier Furthermore, on a tissue weight basis the fetal heart of guinea pigs had six times the concentration of unchanged digitoxin as the maternal heart This then led us to wonder whether a similar *phenomenon occurs in human subjects and if so whether the* concentration in the fetus has deleterious effects A speculation also arises as to whether an increased concentration of the glycoside in the fetal heart can have pathological effects directly on the myocardium as demonstrated in experimental animals after chronic administration of digitalis [7-31]

A Method of Study

Four pregnant women who were hospitalized in the Chicago Lying in Hospital were selected for this investigation Three of the women underwent therapeutic abortion of the fetus for various clinical reasons during the eleventh and twelfth week of gestation The fourth woman carried an anencephalic monster to delivery Three to five hours before hysterotomy the first three women were given carbon 14 labeled digitoxin intravenously in doses of either 0 25 or 0 5 mg A dose of 0 5 mg was administered to the fourth woman at two to three hours before the expected time of delivery In this case the fetal heart beat stopped during delivery two hours after administration of the drug The still birth occurred during the thirty fourth week of gestation

Maternal and fetal cord blood and various fetal organs were obtained All tissue samples were removed as quickly as possible after expulsion of the fetus rinsed thoroughly with saline frozen at once with dry ice and stored at —17 C The extraction procedure for the labeled compounds was similar to those discussed earlier

B Per Cent of Injected Dose in Fetus

The data in Table III indicate that a small amount of the cardiac glycoside crossed the placental barrier as evidenced by its presence in the fetus Less than 0 1% of the injected dose was found as unchanged digitoxin and less than 0 33% was found as

gm of tissue as compared with 11 6 and 7 1 microgm per 100 gm for the heart and kidney respectively of eleven to twelve week fetuses

It is worthy of note that hepatic excretion of digitoxin and its metabolites can be demonstrated in the near term fetus by the presence of these compounds in the liver gallbladder and intestine

D Concentration of Digitoxin in Fetal Heart vs Adult Myocardium

Since it was not possible to obtain samples of maternal myocardium a direct comparison could not be made on the concentration of digitoxin in the maternal and fetal heart However in a separate experiment a sample of an adult auricular appendage was

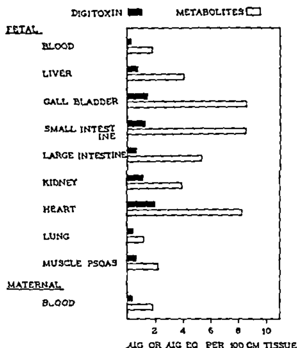


Figure 11 Concentration of radioactive digitoxin and its metabolites in human fetal organs at 34 weeks of gestation One half mg of labeled C^{14} digitoxin administered intravenously 2 hours before death that occurred during delivery

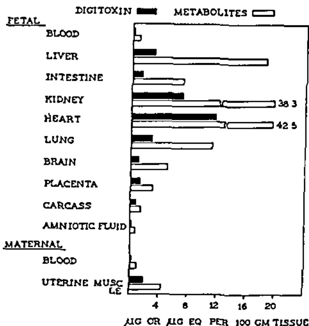


Figure 10 Concentration of radioactive digitoxin and its metabolites in human fetal organs at 11 to 12 weeks of gestation One half mg of labeled digitoxin administered intravenously 2 8 to 5 hours before therapeutic abortion Fetal tissues obtained from the patient receiving 0 25 mg were corrected for 0 5 mg dose All figures represent the average value from tissues of three fetuses Figures 10 11 12 reproduced from article to be published in *Circ Res* by Okita Courtesy Grune & Stratton Inc

near term fetus is shown in Figure 11 The concentration of the drug and its metabolites in the organs that were selected for study is lower in general than that found in the organs of the eleven to twelve week fetuses Part of this difference may be accounted for if the concentration of the drug is expressed in terms of its distribution per cell since fetal cells are smaller in size during the eleventh and twelfth week of gestation than during the terminal stages of pregnancy The organs with the highest concentrations of the unchanged drug were the heart gall bladder small intestine kidney and liver The values for these organs ranged between 0 8 to 2 0 microgm of digitoxin per 100

may be summarized as follows After intravenous administration of digitoxin there is a rapid initial removal of the drug from the vascular system as evidenced by the disappearance of approximately 60% of the drug from the blood stream within fifteen minutes after its administration Once the digitoxin blood level has equilibrated with body tissues the drug is gradually released from its site of deposition into the general circulation over a period of up to twenty three to fifty days During as well as after the initial blood tissue equilibration period some of the drug is meta

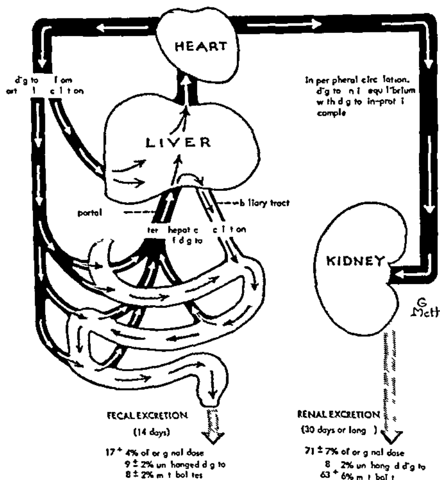


Figure 12 A diagram representing a hypothetical scheme of the metabolic fate of radioactive digitoxin in human subjects

TABLE IV

AMOUNT OF C^{14}-DIGITOXIN AND ITS METABOLITES IN HUMAN FETAL HEART AND ADULT AURICULAR APPENDAGE

Tissue	*Dose (Mgm.)*	*Time After Injection (Hrs.)*	*Digitoxin (Ugm. Per 100 Gm. Tissue)*	*Metabolites (Ugm. Eq. Per 100 Gm. Tissue)*
Fetal heart (12 week gestation)	0.5*	2.8–5	11.6	42.5
Fetal heart (34 week gestation)	0.5	1.7	2.0	8.2
Adult auricular appendage	0.5	3	1.1	2.5

* Fetal tissue obtained from patient receiving 0.25 mg. dose was corrected for 0.5 mg. dose.

obtained from a patient undergoing cardiac surgery. One half mg. of C^{14} digitoxin was administered intravenously three hours before removal of the myocardial tissue. A comparison of the concentration of labeled digitoxin and its metabolites in the fetal heart with that in the adult auricular appendage is given in Table IV. The heart of the near term fetus has approximately twice as much of the unchanged drug as the adult auricular appendage while the concentration in the hearts of the eleven to twelve week fetuses is approximately ten times greater. Here again this difference may possibly be explained on the basis of differences in cell size. Wollenberger[3] has postulated that mature and immature cells may have roughly the same number of drug molecules per cell but differ on a tissue weight basis. Therefore Wollenberger believes that this may account for his findings that the heart of immature experimental animals is able to tolerate a larger dose of ouabain than that of mature animals.

If Wollenberger's findings can be extrapolated to human beings, it seems likely that the minute amount (less than 1%) of digitoxin that crosses the human placenta may be considered to be non-toxic to the unborn child.

METABOLIC FATE AND PATHWAY OF DIGITOXIN

A diagram representing a hypothetical scheme of the possible course of events of digitoxin in man is shown in Figure 12. Briefly, the metabolic fate and pathway of the cardiac glycoside

Tissue distribution studies demonstrate that the myocardium has no preferential affinity for the cardiac glycoside over the other organ tissues analyzed On a tissue weight basis the kidney and contents of the gallbladder, jejunum ileum and colon had a higher concentration of the unchanged drug than did the cardiac tissue It is worthy of note that almost all of the organs assayed had a higher concentration of metabolic products than the parent compound The majority of the administered glycoside was metabolized in the body with the liver being the main organ involved in the detoxification of the cardiac drug However biliary excretion is believed to play only a minor role in the elimination of digitoxin

Renal excretion curves indicate that there is a rapid initial decline in the amount of labeled compounds eliminated per day followed by a gradual leveling off of the curve During the initial three day period 20% of the administered dose is eliminated as total carbon 14 with about half of this amount being excreted during the first twenty four hours Biological half life calculation for the unchanged drug was found to be approximately nine days with a turnover time of thirteen days Minute amounts of the parent compound were detected up to twenty three to fifty days after administration of the glycoside depending upon the dosage used Metabolic products of digitoxin have been assayed in the urine up to thirty one to eighty days Approximately 8% of the administered glycoside was excreted in the urine in the unchanged form and approximately 71% as its metabolic products Fecal excretion studies demonstrated that only 9% and 8% respectively of the original dose was eliminated in the feces

Placental transfer experiments with the labeled glycoside showed that less than 1% of the unchanged drug and less than 3 5% of the metabolites could be detected in the fetus between 1 7 to 5 hours after injection of the labeled drug to the mother

A hypothetical scheme of the possible metabolic fate and pathway of digitoxin in human subjects has been described

ACKNOWLEDGMENT

This review includes data which was obtained earlier by the joint efforts of other colleagues in this laboratory These include Drs E M K Geiling P J Talso F L Kelsey E J Plotz M E

bolized by the liver with a portion of both the glycoside and its metabolites entering the gastrointestinal tract via the biliary route A large percentage of the metabolites and some of the digitoxin in the gastrointestinal tract are then reabsorbed by the small intestine and enter the entero hepatic cycle From the general circulation small amounts of the metabolic products and lesser amounts of the unchanged drug are continuously removed from the vascular system by the kidney Eventually approximately 71% of the original dose is excreted in the urine as metabolic products and approximately 8% as unchanged digitoxin Fecal excretion accounts for approximately 9% of the original dose is the unchanged drug and 8% as metabolic products Therefore the main organ involved in the ultimate excretion of the labeled compounds is the kidney However if only the unchanged drug is considered the amount excreted in the urine is approximately the same as that excreted in the feces The long biological half life of approximately nine days for digitoxin thus confirms the well known cumulative action of the cardiac glycoside

SUMMARY

Using the isotope tracer technique a quantitative study was made of the blood level tissue distribution excretion and placental transfer of intravenously administered radioactive digitoxin in human subjects The sensitivity of the radioactive method permits one to isolate and detect as little as 0 02 microgram of labeled digitoxin provided non labeled digitoxin is added as carrier to the biological sample to aid in the isolation of the labeled compound

Blood level studies indicate that within two minutes after administration of 0 5 or 1 2 to 1 5 mg of C^{14} digitoxin approximately 42% of the injected dose can be detected in the circulating blood as the unchanged drug One hour later only 6% can be detected Calculation for the biological half life of the two exponential rate components shows that the fast component has a $t_{1/2}$ of fifteen to thirty minutes while the slower component has a $t_{1/2}$ of forty eight to fifty four hours It is believed that a third component representing the disappearance rate of "firmly" bound digitoxin with a longer half time can be demonstrated if the blood concentration was followed for a longer period

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Davis Messrs J H Curry Jr and F D Smith Jr to whom the author wishes to express his indebtedness and gratitude The author also wishes to acknowledge appreciation to Drs W H Adams and E B Bay for their cooperation in providing patients for this study and to Dr R W Wissler for conducting the autopsies

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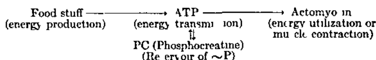
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work For any muscle to do work it must have a *ready* and *specific* source of energy This energy source is initially from ingested food However within the cell this energy in the food must be transmitted into work (muscle contraction) The final source of energy within the cell is believed to be a phosphate bond and more specifically the terminal phosphate of adenosine triphosphate (ATP) This is expressed symbolically as ~P (*high energy phosphate bond*) 11 000 to 12 000 calories of energy in this bond become available as motion and work when ATP reacts with actomyosin



Skeletal muscle differs from heart muscle in its content of ATP (and phosphocreatine) The concentrations of these two substances in skeletal muscle is ten fold greater than in heart muscle This greater concentration of ATP and PC and also of enzymes which can operate anaerobically means that skeletal muscle can for short periods of time operate at an oxygen deficit This system is obviously called into play during sudden and severe activity when the energy demands of the skeletal muscle for oxygen could not possibly be met During such an interval the energy for muscular contraction is made available through an anaerobic cycle and an oxygen debt is established

Heart muscle by its very nature must have an energy source which can provide a sustained energy from the foods stuffs and oxygen Cardiac muscle is relatively poor in ATP and PC but rich in oxidative enzymes During oxidation the bulk of the energy of the food stuffs is made available as ATP The tremendous vascularity of cardiac muscle protects the heart under normal conditions by giving it a constant supply of oxygen Thus *the heart muscle is ideally prepared for sustained* transformation of potential energy into muscle contraction

From the medical point of view the best known and most important effect of digitalis is its ability to increase the *working capacity* of *heart muscle*

The "heart lung preparation is frequently used as an ex

A Discussion on the Site of Action of Digitalis

SANTIAGO GRISOLIA M D *
AND
NOBUO ITO M D

WE HAVE DECIDED to approach this discussion from the bio chemical viewpoint because of our belief (with some latitude) that the cell is a complete and independent living system and as such can be used as a model to understand the action of multi cellular organs such as the heart

The first question one should ask in attempting to analyze the site of action of digitalis is where do digitalis and the meta bolic products of the drug accumulate in the body? Considerable information in this regard has been gained by using radioactive digitalis Surprisingly the liver accumulates about three times as much digitalis and ten times as much digitalis metabolites as does the heart [1] This work confirms earlier reports showing that the heart possesses no great specificity for the drug [3]

In spite of this lack of specific affinity of heart muscle for digitalis it is the heart which is benefited by digitalis and it is the heart muscle which must be studied (However before dis cussing this point it should be noted that we cannot as yet be sure that it is unaltered digitalis which acts on the heart The possibility of metabolites formed from digitalis in the liver or other organs having a cardiac action cannot be excluded The marked differences in speed of action of the various digitalis products certainly suggests that these differences reflect distinct enzymatic mechanisms of transfer transformation or degrada tion)

The main difference between skeletal and cardiac muscle is in the manner in which each muscle maintains the capacity for

From the McIlvain Cardiovascular Research Laboratory University of Kansas Medical Center Kansas City Kansas

The supernatant fraction (presumably containing the bulk of the *myosin*) had very little activity only 0 2%

Furthermore using their data it is possible to calculate roughly using a molecular weight of 100 000 for heart myosin [9] and the data of Okita *et al* [1] for total fixed digitoxin that the interaction of myosin with digitoxin would entail a molar rela tionship of 1 10^{8} (assuming a single site of action) Chemical reactions of this dilution make a *digitalis myosin therapeutic relationship* somewhat unlikely

Therefore the possible action of digitalis at the *energy pro duction* or *transfer level* rather than the *actomyosin level* should be considered also

As indicated above measurements of respiration alone do not permit a clear understanding of biochemical events in fact the literature on digitalis is full of contradictory evidence in this regard

We have therefore studied the possible action of digitalis at the site of energy production Our studies have been with the

TABLE I

THE EFFECT OF DIGITOXIN AND QUINIDINE UPON DNP UNCOUPLING OF OXIDATIVE PHOSPHORYLATION

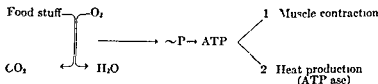
Each vessel contained the following expressed in micromoles per 2ml potassium phosphate buffer pH 7 45 30 tris-HCl buffer pH 7 5 100 potassium α-keto-glutarate, 30 sodium ATP 4 $MgSO$ 15 glucose 100 rabbit heart mitochondria 0 7mg nitrogen per vessel added in 0 5ml of 0 25M sucrose Enough hexokinase to transfer 150 micromoles of high energy phosphate per ten minutes at 38 Hexokinase and DNP tipped after equilibration (ten minutes) sixteen minutes incubation at 38 Air NaOH in center well

Exp	*Conditions*	*O Uptake*	*P O*
1	Control	6 2	2 60
1	+ DNP 1 25 10^{-5} M	5 6	2 36
1	+ DNP 5 10^{-} M	6 2	1 89
1	+ Digitoxin 3 3 10^{-6} M	6 6	2 40
1	+ Digitoxin 3 3 10^{-} M + DNP 1 25 10^{-} M	6 3	1 91
1	+ Digitoxin 3 3 10^{-} M + DNP 5 10^{-} M	6 8	0 76
1	+ Digitoxin 6 6 10^{-6} M	6 2	2 40
1	+ Digitoxin 6 6 10^{-6} M + DNP 1 25 10^{-5} M	5 5	1 64
1	+ Digitoxin 6 6 10^{-} M + DNP 5 10^{-5} M	7 4	0 72
2	Control	6 9	2 60
2	+ DNP 1 25 10 M	6 8	2 40
2	+ DNP 5 10^{-} M	7 3	1 46
2	+ Quinidine 5 10^{-4} M	3 9	2 80
2	+ Quinidine 5 10^{-} M + DNP 1 25 10^{-6} M	3 6	2 15
2	+ Quinidine 5 10^{-4} M + DNP 5 10 M	4 1	0 81

perimental tool in the study of the effect of digitalis on the contracting mechanism of the heart With this technique it has been noted that following digitalis there is increased force of contraction without an increase in oxygen utilization This has been interpreted as indicating an increased *efficiency* in the muscle contraction (actomyosin)

However, another explanation is possible Cells appear to possess an energy regulating mechanism which permits the cell to use its energy for either *work* (muscle contraction or other energy requiring functions) or for *heat production* Mammalian cells and particles from them (mitochondria) if briefly incubated in the absence of substrate will have marked increase in heat production (ATP ase activity) A normal preparation can increase respiration over its baseline either by making the cell do more constructive chemical work or by increasing the energy lost by ATP ase or ATP ase like action with heat production

Perhaps in the heart lung preparation the preparation acts as a damaged cell and upon depleting the necessary substrates and co enzymes simply tends to shift its activity into *heat production* instead of *work production* Then the beneficial effect of digitalis may not be directly on the actomyosin but by in some manner expediting the effective utilization of the high energy phosphate (~P)



The sum of processes 1 and 2 might be responsible for automatic regulation of respiration If process 2 increases at the expense of 1 then no effect on the total respiration will occur

The site of accumulation of digitalis in the heart has been referred to earlier in this discussion In heart perfusion experiments by Harvey and Pieper [8] it was learned that the greatest concentration of digitoxin was in the fraction of the cell representing "*nuclear*" *cell membrane* and "*mitochondrial* fractions

sides affect rather profoundly the permeability of the intact cell but not of the mitochondria *with respect to* Na^{+} *and* K^{+} while 2 4 dinitrophenol affects permeability of these ions in both the intact cell and the mitochondria [11] To obtain further information for the understanding of this phenomena we have studied a the effect of digitoxin upon the ATP ase activity of mitochondria and b the effect of digitoxin upon oxidative phosphorlyation of mitochondria after aging

a ATP ase activity was measured in fresh preparations and after aging with and without Mg^{++} present The results shown in Tables III and IV indicate that the ATP ase activity is not *affected under these conditions by digitoxin*

b The ability of aged particles of the cell to keep good oxidation with loss of phosphorylating ability have been shown by a number of investigators We have found as in earlier work [1] that the aging effect on phosphorylation is very dependent upon the concentration of the cell fraction and also on the suspending medium The sarcosomes of the pigeon heart muscle are best protected by sucrose as shown in Table V

TABLE III

ATP ASE ACTIVITY OF RAT LIVER MITOCHONDRIA WITH AND WITHOUT DIGITOXIN

Condition	*Aging Time in Minutes*							
	0		*20*				*30*	
	I	*II*	*I*	*II*	*I*	*II*	*I*	*II*
	μM	μM	μM	μM	μM	μM	μM	μM
Control A	1 04	1 85	74	3 58	58	3 36	—	—
$+ 3\ 1 \times 10^{-}$ M Digitoxin	1 08	2 10	68	3 40	60	3 50	—	—
$+ 1\ 56 \times 10^{-}$ M Digitoxin	1 21	2 22	81	3 61	72	3 54	—	—
Control B	87	1 38	83	2 82	—	—	74	3 46
$+ 3\ 1 \times 10^{-4}$ M Digitoxin	92	1 63	88	2 94	—	—	82	3 41
$+ 1\ 56 \times 10^{-4}$ M Digitoxin	1 02	1 83	90	3 22	—	—	96	3 56

ATP ase activity tested in all cases using conical 12ml tubes incubated at 38 for ten minutes using a final volume of 2ml containing the following components expressed in micromoles ATP 8 Tris buffer pH 7 4 100 Control experiments received 0 1ml of ethanol Digitoxin was added in the same volume of ethanol Mitochondria concentrations in mg nitrogen per tube 0 35 for experiments of column I 1 05 for experiments of column II Inorganic phosphate liberated is expressed in the table in micromoles

TABLE II

THE EFFECT OF SODIUM AND POTASSIUM CONCENTRATION UPON OXIDATIVE PHOSPHORYLATION AND DIGITOXIN POTENTIATION OF DNP UNCOUPLING ON LIVER MITOCHONDRIA

All components were as described for the experiments of Table I except that α-ketoglutarate was replaced by L-glutamate and that 0.027 micromoles of cytochrome c were added to each vessel. In experiment 2A 90 micromoles of KCl were added. In experiment 2B potassium was entirely replaced by sodium. Guinea pig liver mitochondria 1.7mg nitrogen for experiment 1, 1.8 for experiments 2A and 2B. Fifteen minutes incubation at 38.

Exp	*Conditions*	*O Uptake*	*P O*
1	Control	5.6	2.2
1	+ DNP 1.25 × 10^{-5} M	5.6	2.1
1	+ DNP 5 × 10^{-5} M	6.1	1.9
1	+ Digitoxin 3.3 × 10^{-5} M	6.2	2.0
1	+ Digitoxin 3.3 × 10^{-5} M + DNP 1.25 × 10^{-5} M	7.3	1.5
1	+ Digitoxin 3.3 × 10^{-5} M + DNP 5 × 10^{-5} M	7.3	1.3
2A	Control	7.9	2.2
2A	+ DNP 1.25 × 10^{-5} M	7.5	2.2
2A	+ DNP 5 × 10^{-5} M	8.9	1.5
2A	+ Digitoxin 3.3 × 10^{-5} M	8.9	2.2
2A	+ Digitoxin 3.3 × 10^{-5} M + DNP 1.25 × 10^{-5} M	9.2	1.8
2A	+ Digitoxin 3.3 × 10^{-5} M + DNP 5 × 10^{-5} M	9.6	1.5
2B	Control	3.2	0.8
2B	+ DNP 1.25 × 10^{-5} M	3.1	0.8
2B	+ DNP 5 × 10^{-5} M	4.3	0.4
2B	+ Digitoxin 3.3 × 10^{-5} M	4.2	0.6
2B	+ Digitoxin 3.3 × 10^{-5} M + DNP 1.25 × 10^{-5} M	3.6	0.6
2B	+ Digitoxin 3.3 × 10^{-5} M + DNP 5 × 10^{-5} M	3.5	0.1

major energy producing fraction of the cell, that is, with the mitochondria (sarcosomes) and to observe the influence of digitoxin on normal mitochondria and on mitochondria damaged in a number of ways. In this manner by measuring oxygen uptake and phosphate esterification it is possible to obtain a good idea of the energy production.

In our own investigations we have found[10] that although digitoxin and quinidine at fairly high levels do not affect appreciably the energy production of normal mitochondria they potentiate the uncoupling effect of DNP as seen in Tables I and II.

It is then apparent that the potentiating effect of digitoxin and quinidine upon the DNP uncoupling of oxidative phosphorylation reflects an effect somewhere in the energy respiratory chain (whether or not by affecting permeability is not known) and that this effect is markedly dependent upon the ionic composition of the medium. In this regard it has been shown that cardiac glyco

ily connected with the contraction of muscle it might yet be connected to the utilization of ATP as for example in the hypothetical case that ATP were deaminated* after interaction with actomyosin and that the resulting ITP** had to be reaminated from aspartic or glutamic acid or glutamine (as in the reaction inosinic acid + aspartic acid→adenylic acid) at the expense of the energy of ATP [1] This hypothesis might not be entirely off since after all the 6 amino group of adenine in the nucleotide form is known to be very rapidly equilibrated with isotopic ammonia [2]

TABLE VI

THE EFFECT OF DIGITOXIN UPON OXIDATIVE PHOSPHORYLATION OF FRESH AND AGED SARCOSOMES

Aging Time at 20	*Molarity of Digitoxin*	*O_2 Uptake*	*P O Ratios*
min		μ atoms	
0	0	3 02	2 57
0	3 1 (1 25) × 10	2 93	2 78
5	0	1 46	2 28
5	3 1 (1 25) × 10^{-6}	1 48	2 02
10	0	1 52	1 53
10	3 1 (1 25) × 10^{-6}	1 17	1 39
15	0	1 77	0 68
15	3 1 (1 25) × 10^{-6}	1 56	0 85

Each Warburg vessel (ca 7ml total volume) contained the following components expressed in micromoles in 1 0 ml Potassium a Ketoglutarate 16 5 ATP 2 2 Potassium phosphate buffer pH 7 4 11 Tris buffer pH 7 4, 28 MgSO 5 5 glucose 50 Enough Hexokinase to transfer 75 micromoles of high energy phosphate per ten minutes at 38 Air NaOH in center well Incubation at 38 for twelve minutes after eight minutes equilibration Sarcosomes from 3 grams of pigeon heart prepared according to Slater [3] made up to 4 5 ml To each ml of sarcosomal suspension 10 lambdas of ethanol-containing digitoxin were added 0 4ml of sarcosomal suspension were used per vessel The molarity of digitoxin refers to the initial concentration before using the preparations for P/O measurements The figures in parentheses refer to the final concentration obtained after mixing the sarcosomal suspension with the rest of the components in the incubation vessels

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* Very recently Proctor *et al* have shown a marked digitoxin inhibition of ATP deamination in preincubated and thus damaged heart homogenates These interesting experiments should be repeated and extended

** It has become apparent during the last few years that a number of nucleotides might be active in endergonic reactions and further that they might be capable of energetic interconversion [16] as has long been known for ATP ADP via the enzyme myokinase [17] It has also become apparent that the step wise synthesis of the purine and pyrimidine rings require high energy phosphate [15, 19, 20] and that it is possible to achieve the conversion of nucleotides via classical metabolites and co enzymes such as DPN for example in the formation of xanthosine 5 phosphate from inosinic acid [21]

TABLE IV

THE INFLUENCE OF Mg^{++} ON THE ATPASE OF RAT LIVER MITOCHONDRIA WITH AND WITHOUT DIGITOXIN

Aging Time		Molarity of Digitoxin		
		0	3 1 × 10^{-4}	1 56 × 10^{-4}
min				
0	(A)	1 32	1 08	1 48
25	(A)	2 25	2 22	2 13
0	(B)	1 43	1 45	1 45
25	(B)	2 28	2 23	2 40

Experimental conditions were as described for the experiments of Table III except that the tests were carried out in the presence of 0075 M Mg SO_4 (Experiments A) and 01 M (Experiments B) 0 9mg mitochondrial nitrogen for each tube

The respiration and phosphorylating ability of fresh and aged sarcosomal preparations is not affected by digitoxin under our experimental conditions as shown in Table VI

The utilization of ATP during a single muscle twitch has been challenged[4] It has been shown also that other nucleotides (for example uridine triphosphate[1]) can replace ATP and that on a molar basis they are equal both in inducing contraction and re laxation in an *in vitro* model system

It is warranted to postulate that if a compound X is primar

TABLE V

THE EFFECT OF SEVERAL CO-FACTORS UPON OXIDATIVE PHOSPHORYLATION OF NATIVE AND AGED MITOCHONDRIA

Suspending Medium	P/O Ratios	
	Aging Time in Minutes at 20	
	0	10
Isotonic Sucrose	2 02	2 25
1 1 Isotonic Sucrose KCl	2 17	1 36
1 1 Isotonic Sucrose-NaCl	1 73	1 29
1 1 Isotonic Sucrose Cocktail #1	2 38	1 09
1 1 Isotonic Sucrose Cocktail #2	2 36	1 55
1 1 Isotonic Sucrose Cocktail #3	2 38	1 57

The components and experimental conditions were as for the experiments described in Tables III and IV except that sarcosomes were prepared as previously described[10] and washed one additional time Sarcosome nitrogen 0 625 mg per vessel Cocktail #1 contained 01M Mg SO 001M DNI 025M ATP and 015M Tris buffer made isotonic with sucrose cocktail #2 and #3 had the same composition except that the medium contained half isotonic KCl or NaCl at the expense of isotonic sucrose

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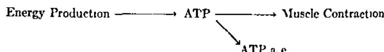
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The experimental data presented in Tables I and II has been reported previously [10]

CONCLUSION

In conclusion and according to the simplified scheme



1 It is known that digitoxin has a marked effect on contraction of damaged muscle from clinical and physiological evidence

2 The therapeutic action of digitoxin might occur at site 1 or 2 or both as indicated

3 *The toxic effect of digitoxin might be related to 1 when* the cell has been already damaged as for example with DNP

Although it is not necessarily true that a toxic effect and a therapeutic effect have the same point of action we should certainly be aware of the necessity of evaluating biochemical effects of digitoxin only after testing in damaged heart preparations (or but less convincing is preventing damage) While the experiments reported here appear to have little significance for therapeutic interpretation of the site and mechanism of action of digitoxin they might indicate the basis for the toxic effects of digitoxin It should be emphasized at this point that mitochondria forms a small portion of the cardiac muscle cell It appears then of importance to continue this experimental approach and to keep in mind the possibility that digitoxin and related substances might act after metabolic conversion to other compounds

It should also be kept in mind that the techniques thus far used might not be adequate to prove experimentally the mechanism *of action of digitalis and in this way to clarify the primary* cause of cardiac failure However only by trying our best can we expect to go ahead and thus I think it fitting to close with the words of Withering

These remarks consist partly of matter of fact and partly of opinion The former will be permanent the latter must vary with the detection of error or improvement of knowledge I hazard them with diffidence and hope they will be examined with candour not by contrast with other opinions but by an attentive comparison of the phenomena of disease"

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Effects of Cardiac Glycosides on Systolic Contraction and Resting Length of Ventricular Strips

Aldo A Luisada M D
and
Christ Aravanis M D

Various plants contain substances whose action on the myocardium *is similar to that of digitalis For this reason their active* principles are called *digitalis bodies* in spite of their different origin The most important are the active principles of *digitalis purpurea digitalis lanata* and *strophantus Kombe*

The advances in the chemistry of digitalis glycosides of the last twenty years finally resulted in their isolation

Scheme I simplifies a more complex detailed scheme of *Stoll*[1] and describes the glycosides of the two main digitalis plants Strophanthin K *is the complex of active principles of strophanthus* Kombe

Several of the glycosides are claimed to be supplied in pure form by various pharmaceutical houses However many commercial *preparations represent mixtures of glycosides* Those which seem the most reliable and have a fairly constant composition are shown in Table II with the indication of the content of each glycoside

Both aspects of ventricular function can be studied in isolated papillary muscles or ventricular strips

Systolic contraction is better studied by using an *isometric method* which submits the strip to a determined initial tension On the contrary *diastolic length* is better studied by using an *isotonic method* which allows the fibers to adjust at the length set by their biochemical processes without any stretching The first method has been extensively used by *Cattell* and *Gold*[2,3] and many others while the second has been employed by the author and his coworkers[4,5]

Working on isolated papillary muscles of the cat and using an isometric system *Cattell* and *Gold*[1,3] studied the effect of several solutions of cardiac glycosides They paid attention only to the amplitude of systolic contraction determined by electric stimulation Solutions of Ouabain or Digitoxin of 1 100 million were found ineffective Solutions of 1 10 million or 1 20 million acted promptly and caused a marked increase of systolic contraction

TECHNIQUE

Our experiments were performed on isolated papillary muscles or right ventricular strips of large cats or small dogs removed under Nembutal anesthesia

The cardiac strip was placed in a vessel containing Locke s solution at 38 C immersed in a constant temperature bath and was stimulated with 150 v shocks from an Electrodyne stimulator The stimulator was connected to a fine platinum wire inserted into the muscle strip just above the level of the fluid and to a metal blade placed into the solution Solutions to be tested were prewarmed through immersion in the water tank Oxygen flow was stopped just prior to taking a record in order to avoid artifacts

The strip was attached to a fixed point at its lower end and at its upper end to a light isotonic lever

The lever covered with a strip of black paper was interposed between a source of light and a phototube The latter was connected with a string galvanometer and the string calibrated at 2 cm /1 mv The polarity was so arranged that a shortening of the muscle caused a drop of the light beam on the film The movements of the muscle strip were magnified twenty five times so that quantitative evaluation of the shortening or elongation of the cardiac strip was possible

Stimulation was considered necessary in order to ascertain the viability of the muscle and the effect of drugs Therefore each cardiac strip was stimulated at a rate of 60 shocks/min After obtaining throughout the experiment a control record of diastolic length and amplitude of contractions stimulation and oxygen flow were discontinued and a second record was taken showing only the resting length In general a double record (with and without

stimulation) was obtained every five to ten minutes throughout the entire experiment As the strips presented variations of length during the first twenty to thirty minutes the actual study started after such period of time

Electrograms of the muscular strip were recorded by means of a second string galvanometer The silver wire stuck into the upper end of the strip (above the fluid level) and the metal plate within the fluid were used as electrodes Electrograms were recorded only during periods in which no electric stimulation of the strip was used

In order to avoid the effect of suspension of the oxygen flow electrical changes were also studied with the strip immersed in heparinized blood

The leads were so arranged that the zero line was at the lower level of the film so that the *injury current* inherent in the preparation would bring the tracing *upwards* toward the center of the film

Drugs were tested by rapidly substituting the Lockes solution in which the strip was bathed with the prewarmed solution containing the drug In most experiments only one drug was tested at that concentration which had been found effective in preliminary tests A tracing was obtained immediately after changing the solution then again at five to ten minute intervals

However a comparative evaluation of the activity of two drugs was occasionally attempted by testing them in succession *in similar concentration Then the experiment was repeated* on another strip using the drugs in the reverse order

RESULTS

General Effect of the Drugs Adequate concentrations generally caused a shortening of the muscular strip The effect usually started ten to fifteen minutes following the change of the solution and reached its maximum within thirty to forty five minutes Occasionally, a minimal relaxation took place in the first five to eight minutes prior to the onset of the contraction

The effect of the drugs on the resting strip was frequently revealed by *small rapid contractions* (Figure 1A C) These were sometimes regular and periodic and at times were followed by

incomplete relaxation (Figure 1A). In a few experiments the drug caused a rather rapid and steady shortening of the strip (Figure 1B).

The amplitude of the rapid contractions caused by electric stimulation was frequently increased by cardiac glycosides. However, *no constant relationship was found between increase or decrease in amplitude of these rapid contractions and the steady slow contracture of the strip*, except for decrease in amplitude occurring whenever the contracture was extremely severe.

Effect of Ouabain. Ouabain was the drug tested in the great

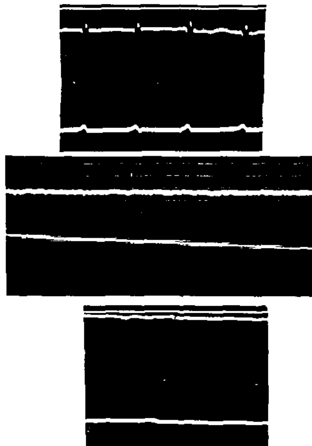


Figure 1. (See text.)

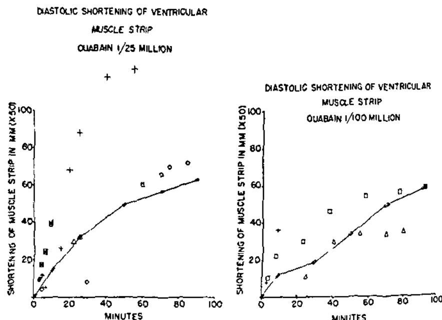


Figure 2 (See text)

est number of experiments. *Solutions ranging from 1:15 million* to 1:250 million were tried. The action of the drug manifested itself within five to eight minutes and consisted of a gradual steady contraction revealed by a shortening of the diastolic and resting lengths of the strip. This contraction continued to increase until it reached a maximum in fifty to sixty minutes. The rapidity and degree of the contraction was greater with higher concentration of drugs (Figure 2). The shortening was 2 mm (about 13%) in exceptional cases, 0.75-1.5 mm (5-10%) in most experiments in which a 1:25 million solution was used, and 0.6-1 mm when the concentration of the drug was 1:100 million. In a few experiments the drug caused an initial minimal relaxation followed after five to ten minutes by shortening of the strip.

In general a moderate diastolic shortening was accompanied by temporary increase in the amplitude of systolic contractions upon stimulation. On the other hand a marked diastolic shortening was always accompanied by decrease in the amplitude of systolic contractions and sometimes by a complete lack of systolic response (contracture) (Figures 3, 4). Once this stage was

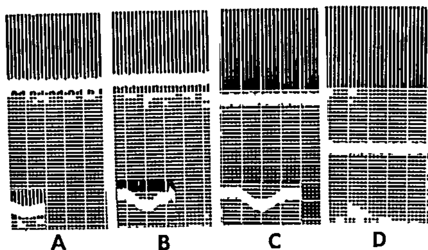


Figure 3 (See text)

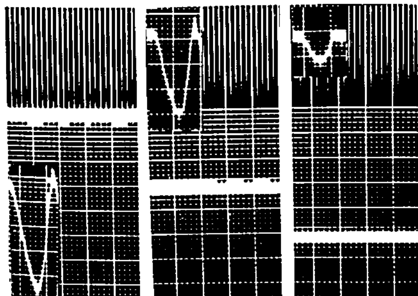


Figure 4 (See text)

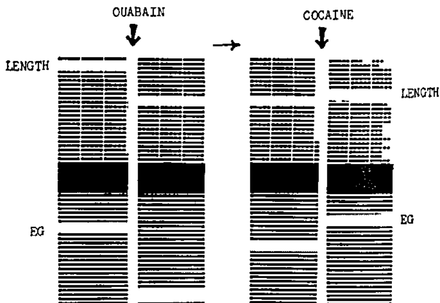


Figure 5 (See text)

reached systolic contractions could still be obtained by (a) increasing the intensity of the stimulus (b) stretching the strip (c) causing a moderate relaxation by means of cocaine (Figure 5) (d) applying a high concentration of epinephrine Epinephrine restored the ability of the strip to contract even though it caused further diastolic shortening

Relative Action of the Glycosides In order to better evaluate the relative action of the glycosides on resting length several cross experiments were performed (Figure 6) The results were as follows Acetyl strophanthidin seemed more effective than ouabain Ouabain was more effective than K strophanthoside While digitoxin and gitalin were equally active in higher concentrations at lower concentrations gitalin had a more powerful action On the other hand digitoxin was more powerful than lanatoside C The relaxation due to digitoxin in low concentration did not prevent the subsequent contracting effect of ouabain Acetyl digitoxin had a contracting effect similar to that of ouabain In lower concentrations it had a relaxing effect even if the drug was used on a strip previously contracted by ouabain

The enhancing effect of the glycosides on the amplitude of the rapid electrically induced contractions seemed independent of the effect on resting length. Actually, it was possible to demonstrate this stimulating effect both with high concentrations of ouabain or digitoxin (which led to shortening of the strip) and with low concentrations of acetyl digitoxin (which were followed by relaxation of the strip).

Clinical Concentrations of Cardiac Glycosides and Effect on Resting Length. The average theoretical concentrations of the glycosides in the blood of clinical cases were calculated in order to compare them with those used in the experiments with ventricular strips. These concentrations were calculated on the basis of the medium and maximum doses received intravenously by patients in the first twenty four hours and on an average blood volume of 5 000 cc.[3]

A comparison of the clinical with the experimental concentrations is presented in Figure 6. It is apparent that most cardiac glycosides are given to patients in doses which should cause a steady shortening of the myocardial fibers and therefore a decrease in cardiac volume. The only exception is represented by

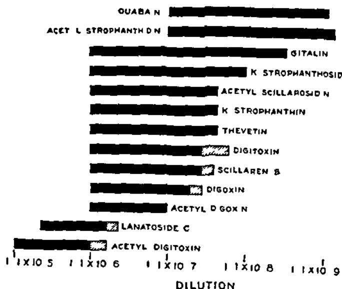


Figure 6 (See text)

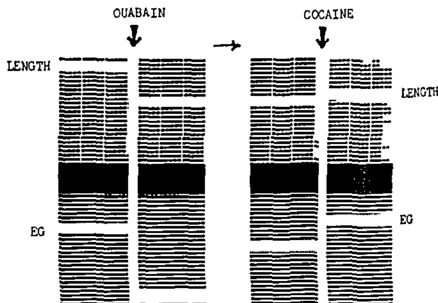


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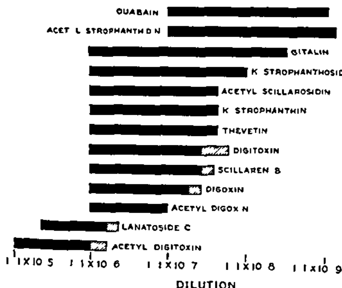


Figure 6 (See text)

acetyl digitoxin which caused relaxation of the myocardial fibers in clinical concentrations A contracting effect of acetyl digitoxin would be obtained only by toxic concentrations

Electric Activity of the Strips The electrographic changes were of various types (a) no evidence of electric complexes while the strip was contracting either slowly or with rapid jerks (Figure 1A B) (b) rhythmic typical complexes immediately followed by mechanical evidence of contraction (action currents) (Figure 1C) (c) a slow continuous change of the baseline co incident *with the slow mechanical contraction (Figure 5)*

Further investigations were made in regard to this slow change of potential In the majority of cases it was a *downward* motion (in the opposite direction of the injury current) *similar to that of the action currents only far slower*

Simultaneous tracings of the mechanical and electrical ac tivities showed a general similarity ouabain in solution 1/10 million caused slow mechanical contraction and electrical evi dence of contraction while acetyl digitoxin in the same solution caused a slow mechanical relaxation and electrical evidence of relaxation *

TABLE I

ACTION OF CARDIAC GLYCOSIDES

Glycoside	*Range of Solutions Causing Decrease of Resting Length (Steady Contraction)*	*Range of Solutions Causing Increase of Resting Length (Steady Relaxation)*
Ouabain	1 5 million to 1 1 billion	
Acetyl strophanthidin	1 5 million to 1 1 billion	
Gitalin	1 1 million to 1 500 million	
K strophanthoside	1 1 million to 1 100 million	
K-strophanthin	1 1 million to 1 50 million	
Thevetin	1 1 million to 1.50 million	
Acetyl cilliro idin	1 1 million to 1 75 million	
Digitoxin	1 1 million to 1 30 million	1 50 million to 1 75 million
Scillaren B	1 1 million to 1 30 million	1 40 million
Digoxin	1 1 million to 1 15 million	1 15 million to 1 25 million
Acetyl-digoxin	1 1 million to 1 10 million	1 10 million to 1 15 million
Lanatoside C	1 200 000 to 1 2 million	1 25 million
Acetyl digitoxin	1 100 000 to 1 1 million	1 2 million or above

* The electric tracings revealed a majority of reactions similar to the mechanical but also a number of unchanged tracings (and even a few with displacement in the opposite direction)

DISCUSSION

Base line changes caused by drugs and indicating changes in resting or diastolic length were recorded by various observers working with either papillary muscles or isolated hearts but were discounted because unexplained by current theories Moreover, in many experiments the base line was brought back to its original level mechanically so that no accurate record of the changes was kept In most cases the investigators used isometric recording which is inadequate for evaluating small changes in length of a strip

Consistent variations of the resting length of a heart muscle preparation (between periods of stimulation) or of its diastolic length (during periods of stimulation) obtained by physiologic or pharmacologic means may be accepted as evidence that these variations are a normal function of the heart muscle Experiments by the author and coworkers proved the possibility of significant changes in the resting and diastolic lengths which were consistently obtained by changes in temperature action of certain ions and that of certain drugs The action of drugs was obtained even in concentrations similar to those which reach the human heart under clinical conditions For example ouabain affects diastolic length in a dilution of 1 250 million the maximum blood concentration obtained after intravenous injection of 0 25 mg is 1 20 million and may drop to 1 250 million several hours later Therefore the results are not due to toxic" effects Similarly the shortening does not appear to be a terminal phenomenon" because a ventricular strip which fails to react to stimulation (contracture) starts again to contract if moderate relaxation is induced by drugs or excitability is increased by means of epinephrine

The action of ouabain on diastolic length had been previously observed but was not evaluated properly It is important to note that the "contracting" effect of this drug can be reversed by cocaine This indicates that cocaine on the one hand and ouabain on the other have opposite actions on a basic property of the heart muscle

Thirteen digitalis preparations were tested on ventricular

acetyl digitoxin which caused relaxation of the myocardial fibers in clinical concentrations A contracting effect of acetyl digitoxin would be obtained only by toxic concentrations

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Thevetin	1 1 million to 1 50 million	
Acetyl-scillirosidin	1 1 million to 1 75 million	
Digitoxin	1 1 million to 1 30 million	1 50 million to 1 75 million
Scillaren B	1 1 million to 1 30 million	1 40 million
Digoxin	1 1 million to 1 15 million	1 15 million to 1 25 million
Acetyl-digoxin	1 1 million to 1 10 million	1 10 million to 1 15 million
Lanatoside C	1 200 000 to 1 2 million	1 25 million
Acetyl digitoxin	1 100 000 to 1 1 million	1 2 million or above

* The electric tracings revealed a majority of reactions similar to the mechanical but also a number of unchanged tracings (and even a few with displacement in the opposite direction)

It is suggested that the action of cardiac glycosides on the diastolic length of the cardiac fibers represents an important part of their clinical effect It is possible therefore that the different effects of various digitalis preparations on resting length consisting of marked shortening (ouabain) moderate shortening (digitoxin digoxin) or even elongation (acetyl digitoxin possibly lanatoside C) may have some bearing on the reaction of different types of patients to digitalization

Various types of electrograms were observed In the first type the muscle contracted smoothly or by small jerks there were either no electrical changes or a slow shift of the base line A second type revealed coordinated rhythmic contractions each preceded by an electric complex apparently a pacemaker had been activated within the strip and governed the activity of the latter

The above studies can be discussed in relation to the problem of cardiac tonus Physiologically muscles can be classified into[6,7] *multi unit muscles* activated by the CNS (skeletal muscles blood vessels muscles) and *visceral muscles* having automaticity (heart various visceral organs) The term tonus has to be applied to fluctuations of the level of tension or length on which brief contractions may be superimposed The mechanism of tonus is not different from that of contraction and involves some expenditure of energy

Studies of the last ten years revealed one type of tonus due to the fact that certain impulses are non conducted because they are too weak and cause only minimal mechanical changes The term tonus should be abolished and substituted by that of resting contraction a phenomenon which may be associated with resting potentials[6,7]

In striated muscles the rapidity of dilatation depends upon a chemical process (probably the resynthesis of the ATP protein complexes) The strength of the intramolecular bindings varies in different types of muscles and it is likely that in this respect cardiac muscle has an intermediate position between the skeletal and the other visceral muscles Bing's observations[8] confirm that cardiac glycosides cause a decrease in the initial length of myocardial fibers Buckley's studies[9] show changes of viscosity in

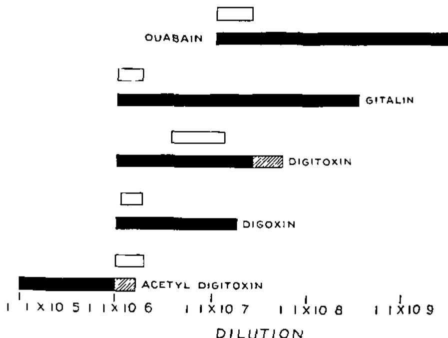


Figure 7 (See text)

strips or papillary muscles in order to study their action on the resting and diastolic length of the strips Striking differences in the results were noted

Ouabain and acetyl strophanthidin were the most powerful causing shortening of the strip even at extreme dilutions On the other hand high concentrations of these drugs seemed to be toxic so that their effect was less apparent

Thevetin scillaren B digitoxin digoxin acetyl scillirosidin and acetyl digoxin were in a second group requiring higher concentration

Lanatoside C and acetyl digitoxin started causing contractions only at high concentrations while they caused a relaxing effect in low concentrations

Comparison of the clinical with the experimental concentrations showed that the contracting effect of most glycosides took place in concentrations which are within the limits of the clinical concentrations On the other hand acetyl digitoxin in clinical concentrations had a relaxing effect on ventricular strips

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7 Bozler E *Am J Physiol* *136* 552 1942 and *167* 276 1951
8 Bing R *et al* *J Clin Investigation* *30* 1951
9 Buckley N M *et al* *Circulation Res* *3* 447 1955

the ventricular wall under the affect of glycosides even though his observations cannot be correlated as yet with those of the present study

SUMMARY

Changes in the length of the resting muscle and in the diastolic length of the contracting muscle were studied in ventricular strips and papillary muscles of mammalian hearts by means of an isotonic lever and photoelectric recording

Spontaneous changes of resting and diastolic length were observed during the first twenty to thirty minutes In exceptional cases periodic undulations were noted Modifications of resting length by effect of temperature or following the action of ions (Ca K) were observed

The ability to change diastolic length seems to be an intrinsic property of the heart muscle independent of hemodynamic influences

Consistent effect of drugs on diastolic length can modify the heart size and should be included among the various pharmacological actions even though it is difficult to evaluate it in normal conditions of the circulation

Ouabain in concentrations ranging from 1 15 million to 1 250 million consistently caused decrease of resting and diastolic lengths (contraction) This shortening reached a maximum of 13%

Thirteen digitalis or digitalis like glycosides were further compared and striking differences were noted in their effect on resting length Ouabain and acetyl strophanthidin were the most powerful Digitoxin digoxin and acetyl digoxin were in a second somewhat less effective group Lanatoside C and acetyl digitoxin were in a third group because they caused relaxation in clinical concentrations while contraction was caused by concentrations which would be equivalent to clinically toxic doses

The electrical manifestations of the ventricular strip were studied Apart from rapid complexes revealing the establishment of a pacemaker two interesting phenomena were noted small jerking shifts of the baseline synchronous with similar jerks of the mechanical tracing or a slow shift of the baseline usually (but not always) in the same sense as that of the mechanical change

of these substances were prepared by us but an overwhelming majority were furnished to us by Professors Reichstein and Stoll of Basel Professor Elderfield of the University of Michigan Professor Tschesche of Hamburg and Professor Frerejacque of Paris The object of our investigation is fivefold (1) The qualitative verification of the digitalis like action of a new substance (2) the quantitative determination of its potency (3) the comparison with its closely related products for structure activity relationship (4) the possibility of its being useful in medicine and (5) any other pharmacological effects of fundamental interest

The simplest way to detect the digitalis like effect is to inject a solution of the substance into the lymph sac of a frog and after an hour to inspect the condition of the ventricle If it stops in systole the result is positive This is the same principle of the old U S P biological assay Just as with digitoxin the response can be recorded graphically by perfusion with an appropriate solution of an active substance Figure 1 shows four sample tracings Divaricoside and desgluco hellebrol in a concentration of 1 500 000 promptly produced A V block and systolic standstill

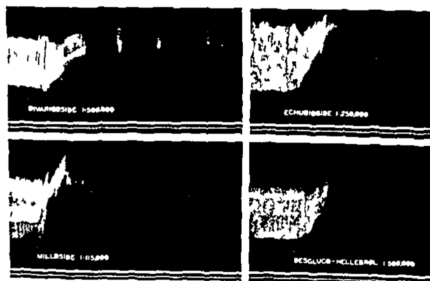


Figure 1

New Chemicals Having a Digitalis-like Action

K K Chen *

This discussion is partly based on the studies carried out in our laboratory It is widely known that digitalis is not the only drug whose active principles have a specific action on the heart There are other sources that yield digitalis like substances and they usually have a long and interesting history From time immemorial peoples of different parts of the world have recognized that the products of certain plants and animals are poisonous Nevertheless they advocated their uses in medicine and other practices although not for heart failure The Greeks and the Arabians were thoroughly familiar with squill and oleander and Dioscorides Hippocrates and Galen mentioned these two plants in their medical works as diaphoretics and diuretics The natives of Africa used the sassy bark as an ordeal in trials for witchcraft They also made arrow poisons out of *Strophanthus* extracts In China for generations the toad venom has been advocated for the treatment of cancer sores sinusitis local inflammation and toothache The be still nuts have been frequently prescribed in the West Indies as an antipyretic emetic and cathartic The lily of the valley had long been employed by the Russians in the control of general anasarca

During the last thirty years rapid progress has been made in chemistry Numerous active principles have been isolated in crystalline form by chromatography from natural sources This technique also serves as an important tool in separating digitalis like compounds from plants and toads The steroidal chemistry has advanced so far that structural formulas of these cardiac substances have been elucidated by competent chemists

In our laboratory during the last twenty five years we have studied pharmacologically some 300 pure compounds 200 of which are natural products and 100 synthetic derivatives Forty

* From the Lilly Research Laboratories Indianapolis Indiana

Brody The procedure involves the intravenous injection of a suitable dilute solution in etherized cats at the rate of 1 cc per minute until death occurs within thirty to sixty minutes In order to be on safe ground we use at least ten cats for the determination of each figure namely the mean lethal dose per kilogram The results appear to be reproducible For example in 1948 we as

TABLE I

NATURAL SUBSTANCES HAVING A DIGITALIS-LIKE ACTION

Source	*Active Constituent*	*Source*	*Active Constituent*
Digitalis purpurea	Digitoxin Gitoxin Digicorin Strospeside	*Scilla maritima*	Scillaren A Proscillaridin A Scillarenin
	Gitaloxin Odoroside H	*Helleborus niger*	Hellebrin
	Glycoside A & B	*Bowiea volubilis*	Bovoside A D & E
D lanata	Lanatoside A B & C	*Urginea rubella*	Rubellin
	Desacetyl lanatoside A B & C Digoxin Digitoxin Gitoxin	*Erythrophleum guineense*	Erythrophlein Cassaine Cassaidine
	Gitorin	*E couminga*	Coumingine
Strophanthus kombe	K Strophanthoside K Strophanthin β Cymarin	*Ch an Su* (toad venom)	Cinobufagin Bufalin Bufotalin Cinobufotalin
S gratus	Ouabain		Gamabufagin Telocinobufagin
S sarmentosus	Sarveroside		Cinobufotoxin
	Sarmentoside A B & C	*Bufo bufo bufo*	Marinobufagin Hellebrigenin
Thevetia neriifolia	Thevetin Neriifolin Acetyl neriifolin	*B arenarum*	Arenobufagin Arenobufotoxin
Cheiranthus cheiri	Cheirotoxin Cheiroside A & H	*B regularis*	Regularobufagin Regularobufotoxin
Adenium Honghel	Digitalinum verum Honghelin	*B quercicus*	Quercicobufagin
	Honghelo side A & C	*B alvarius*	Alvarobufotoxin
Corchorus capsularis	Corchorin Corchoroside A & B	*B valliceps*	Vallicepobufagin Vallicepobufotoxin
Convallaria majalis	Convallotoxin Convalloside		
Mansonia altissima	Mansonin		

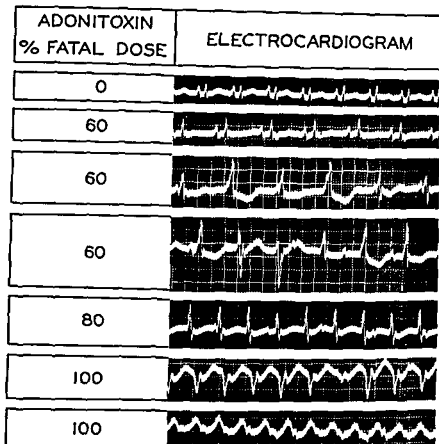


Figure 2 Demonstrates the electrocardiographic change in an etherized cat from the digitalis like action of adonitoxin

Similarly echubioside duplicated the results in a concentration of 1 250 000 and milloside in a concentration of 1 115 000

The electrocardiographic changes of etherized cats during the continuous injection of any active substance are characteristic Figure 2 demonstrates the digitalis like action of adonitoxin The changes are decrease in heart rate prolongation of P R interval flattening of T wave A V dissociation secondary tachycardia and terminal ventricular fibrillation Table I shows an incomplete list of plants and toads which elaborate digitalis like substances

For the estimation of the potency of each compound we have adopted the cat method originally designed by Hatcher and

may be more potent than or equal in activity to its parent glycoside

There are four indispensable portions of the molecule (1) The disappearance of the OH group at C_{14} results in complete loss of activity (2) the hydrogenation of the double bond abolishes the activity (3) rupture of the lactone ring has the same effect (4) change of the asymmetrical center at C_3 C or C_{17} also makes the compound inactive even though the structure appears the same

When we were studying the toad venom we were confronted with the same question that has puzzled most physiologists namely the use of these poisonous glands to the animal Does it use the venom for self protection? The answer is no because the animal does not squirt the venom in time of imminent danger Even if the venom is expressed into the enemy s mouth it will be too late to save its life Then—are the poisonous glands indispensable to the animal? We extirpated the glands aseptically and found these animals to behave exactly the same as normal animals

Another interesting fact is the species difference of response to digitalis and its allies As exemplified by ouabain in Table II the mouse the rat the spadefoot toad and the nebulous toad are resistant in contrast to the cat the guinea pig the rabbit the leopard frog and the tree frog Man is probably the most susceptible animal At one time it was believed that the toad immunized itself with the digitalis like principles of its venom but this is

TABLE II

SPECIES DIFFERENCE OF TOXICITY BY SUBCUTANEOUS INJECTION

OUABAIN

Animal	*Ratio of LD_{50} When Cat is Unity*
Cat	1
Rabbit	2
Guinea Pig	2
Leopard Frog	6
Tree Frog	8
Mouse	62
Spadefoot Toad	418
Nebulous Toad	442
Rat	671

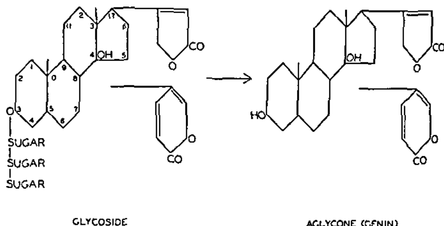


Figure 3 On the left demonstrates a model molecule for a glycoside Note that it is a derivative of the familiar steroid ring system If all the sugar groups are split off the residual structure is called an aglycone (see text)

sayed a sample of digitoxin every month The greatest difference lies between July and October amounting to 18% This is 2% less than the maximum allowed by U S P

Using the cat data as our criteria we may conduct prelimin ary clinical studies with cinobufagin and thevetin The same potency figures can be used for the study of structure activity relationship The formula on the left hand side (Figure 3) is a model molecule for a glycoside It is a derivative of the familiar steroid ring system

In nature the sugars are attached to the secondary hydroxy group at C_3 If it is a single sugar the glycoside is known as a monoside if it is a 2 sugar conjugation it is a bioside if it is a 3 sugar combination it is a trioside etc Pharmacologically the monoside is more potent than the bioside the latter in turn usu ally is more potent than the trioside Among the monosides the kind of sugar often determines the potency Rhamnose or glu cose frequently makes the most active glycoside

When all the sugar molecules are split off the residual struc ture is called an aglycone It is pharmacologically active Both the glycosides and the aglycones have a lactone ring If the lac tone ring is 5 membered the aglycone is always weaker than the parent glycoside If the lactone ring is 6 membered the aglycone

Observations on the Clinical Use of Digitalis

ROBERT C BATTERMAN *

I AM GRATEFUL for this opportunity to crystallize my thoughts on digitalis in the treatment of heart diseases First of all many statements that I will make will probably be controversial and I trust that there will be an opportunity to elucidate some of the problems to everyone s satisfaction

In my presentation there are conclusions based upon a minimum of data The concepts that I shall present have been formulated since 1933 The bulk of the data has never been published In fact some of the data that I shall discuss have never been presented before In most instances the conclusions I believe are justified and others where the data hasn t reached a level of publication I will indicate that the conclusions are tentative

Regardless of whether you believe in the backward or forward failure concepts of heart failure the most important fact to be kept in mind is that the heart muscle has become inefficient It has become incapable of performing its work A balance exists between the amount of work demanded of the heart and the capability of the heart muscle to respond dependent upon the degree of chemical or pathologic abnormalities of the heart muscle or other anatomic components of the heart structure

With this in mind we could then schematically present the course of events in every patient with congestive heart failure as follows (Figure 1)

The functional capacity of the heart muscle or the efficiency in terms of its ability to do the work that it is called upon to do is represented in the vertical ordinate The abscissa represents the duration of the heart disease which is variable It might be short or telescoped into a period of a few days or it might exist for months or years The usual patient begins his cardiac history

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not likely because the mouse and the rat do not elaborate venoms

Finally no information is available about how the plants and toads manufacture their glycosides and bufagins It seems to be no trick for these organisms to run the biosynthetic reactions and come up with not only one but usually several complicated steroidal derivatives On the other hand chemists have made repeated attempts to obtain an active glycoside by complete syn thesis but to date they have not succeeded It apparently in volves more intricate procedures than commonly practiced labo ratory methods

ing two examples a series of clinical possibilities that might be en countered with your patients will be schematically diagrammed

In Figure 2 there are three possibilities dependent upon what stage of functional capacity the patient manifests at the time of the precipitating factor The first or top diagram depicts a patient who because of an overwhelming infection has a temporary de crease in cardiac function The development of signs and symp toms of congestive heart failure classify the patient at this time as functional IV designated by D After the infection sub sides the patient s cardiac reserve is restored again to the same

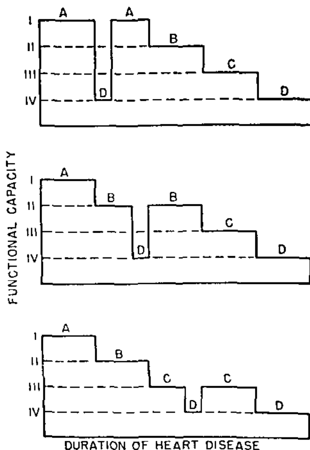


Figure 2

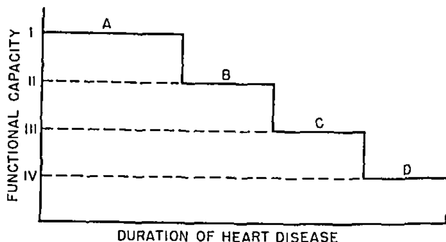


Figure 1

with a functional capacity of I designated as A Although there might be evidence of heart disease upon physical examination x ray determination and/or electrocardiographic abnormalities *there is no disturbance in cardiac reserve The heart of this* patient can do any amount of work required of it without the patient manifesting symptoms or signs of congestive heart failure Sometime along in this patients life span the muscle becomes gradually weakened so that the patient enters the second classification designated as B With a functional capacity of II the patient experiences shortness of breath fatigue but no edema when marked exertion occurs Continuation results in the patient *with a functional capacity of III noted on the graph as C The* slightest exertion now brings forth signs and symptoms of diminished cardiac reserve Edema might appear at this stage Finally the patient will enter the fourth functional capacity designated as D wherein signs and symptoms of diminished cardiac reserve are evident without exertion or upon bed rest This series of events represents a non complicated life span of a patient with heart disease and is never actually seen in practice With rare *exception there is usually a precipitating factor which adds* further stress A heart weakened by an underlying disease process would under such circumstances be incapable of performing its work and a break in compensation would result *In the follow*

available today to determine what the underlying cardiac reserve is Response to therapy is our sole guide for determination of this factor The overall prognosis and subsequent therapy are dependent entirely upon the ability of the patient s heart muscle to perform its work with and without complicating precipitating or aggravating factors

The second point is that practically every patient when they are seen in heart failure has some precipitating factor for that heart failure The usual ones are infections an occurrence of arrhythmias such as auricular fibrillation or attacks of paroxysmal tachycardia excessive exertion excessive intake of sodium or fluid Further damage related to the underlying heart disease

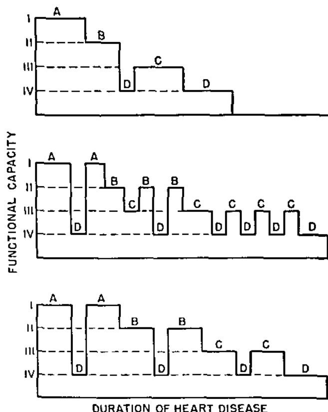


Figure 3

level as existed prior to the precipitating factor The overall picture of the cardiac disease then continued with progressive diminution of the cardiac reserve as would be expected over a period of years

In the second example the patient s heart disease had progressed to a functional capacity of II before the precipitating factor had occurred In the third or bottom illustration the patient was further advanced and had an underlying reserve which clinically reflected itself by dyspnea and fatigue but no edema In both of these cases an infection temporarily reduced the cardiac efficiency to the point where all signs and symptoms of congestive heart failure were present Upon recovery both patients resumed their cardiac reserve existent prior to the acute episode and became ambulatory again

The first illustration of Figure 3 depicts a somewhat different course of events The precipitating factor was an acute bout of rheumatic carditis Following remission the cardiac reserve did not return to the original level as in the previous cases The resultant additional cardiac damage decreased the functional capacity of the heart and thereby influenced the overall prognosis of the patient Similar experiences are noted in patients with repeated bouts of myocardial infarction or multiple areas of progressive myocardial fibrosis regardless of etiology

The next patient had repeated bouts of congestive heart failure during various stages of the heart disease but one in particular warrants comment The second episode or precipitating factor was not severe enough to result in complete decompensation but was only of sufficient intensity to aggravate an already inadequate cardiac reserve to a lower level of efficiency

The final patient demonstrates repeated bouts of failure during each stage of the heart disease

These schematic diagrams give us considerable information in regard to the treatment of congestive heart failure A patient with a complete break in cardiac reserve as noted as D in the foregoing figures might manifest the same degree and type of sign or symptom of congestive heart failure regardless if this episode occurred early or late in the life span of his illness It is thus impossible from the physical examination or any tests

attain this stage as a result of progressive deterioration of heart function In a few instances the life span of the patient may be shortened because of an uncontrollable precipitating factor An overwhelming rheumatic pancarditis or myocardial infarction for example might telescope a stage I cardiac to the terminal phase

An analysis of the course of congestive heart failure according to the above classification parallels the principles applicable to every chronic disease The syndrome of congestive heart failure is no exception Recognition of these principles is of utmost importance for the proper management of the patient with this condition

Particular emphasis should be placed upon the ambulatory or maintenance group of patients These comprise the largest number of patients with congestive heart failure and therefore represent the greatest problem encountered in the use of digitalis Problems of standardization with development of various methods and unitage and techniques for initial digitalization with various digitalis preparations and dosages have been based primarily upon the need for proper management of this maintenance group

Finally the schematic diagrams indicate that the patients response to therapy is dependent entirely upon the underlying reserve existent at the time failure is apparent A patient with a functional classification of III when the acute failure occurred can never respond to the same degree as the patient with an original functional classification of I or II In other words digitalization of a patient in class IV can only be effective if there exists a basic underlying reserve The degree of response is thus a reflection of cardiac capacity to do work and thereby prognosis This concept I believe explains some of the discrepancies found in the literature as to the effectiveness of digitalis for patients with auricular fibrillation or normal sinus rhythm The majority of patients with auricular fibrillation are usually in the first or second stage of their heart disease The onset of the arrhythmia might have been the precipitating factor for the failure However the basic cardiac function is relatively good and with digitalization the response is often dramatic On the other hand most patients with normal sinus rhythm are further advanced in their heart disease usually in stage III and other precipitating factors are

such as rheumatic carditis myocardial infarction etc must be assessed for each patient In the advanced patient inadequate therapy is a very important precipitating factor The patient might of his own accord fail to take his digitalis preparation regularly or might consume additional medication with resultant toxicity and further heart failure Diuretic agents with and without concomitant adjuvants might be inadequately administered It is therefore important to determine what precipitating factor is present in any particular patient and if possible eliminate its existence The treatment of an acute attack of heart failure might not respond to drug therapy unless the precipitating factor is also eliminated Furthermore for future therapy its recognition and steps taken for its control might present not only recurrences of diminished cardiac efficiency but will also result in a more satisfactory management of the patient with chronic congestive heart failure

The third point obtained from these figures is that congestive heart failure as with all chronic diseases may be classified into four phases or groups The first category include those patients who are seen in their initial bout of failure They usually recover and return to the same degree of cardiac reserve before the occurrence of the precipitating factor and the acute decompensation Upon recovery they may be classified as the second group of maintenance or ambulatory patients The third group represents the patient in the ambulatory group who because of a precipitating factor has a recurrence of acute heart failure This is usually a temporary classification When the precipitating factor has been removed the patients recovery of cardiac efficiency has returned the patient to the maintenance group again Unfortunately there are many patients who fluctuate between the maintenance and third group because inadequate measures are taken to control the precipitating factor responsible for the clinical picture Finally the fourth or terminal group of patients represents the type of patient who was designated by D at the extreme right of the previous figures The type of heart disease and whether the pathological process itself was responsible for the poor myocardial efficiency will determine to a great extent the ultimate *duration of this phase As a rule patients in group IV*

RESPONSE TO BED REST

NUMBER OF PATIENTS TO BE TREATED	INCIDENCE OF EFFECTIVENESS	PATIENTS IMPROVED	PATIENTS REQUIRING ADDITIONAL THERAPY
1000	60 /	600	400

Figure 4

toms of the failure The use of these preparations are thus reflective of poor prognosis

Nowadays it is very unusual for any physician or hospital to treat the patients with only bed rest Many times before the patient arrives in the hospital he has received every type of therapy that is available so that it may be difficult if not impossible to do any controlled investigation or obtain a good control group Bed rest alone as the initial form of therapy was an accepted procedure prior to 1935 In many institutions other forms of therapy were held in abeyance until the effects of bed rest alone were evaluated In the studies presented here the number of patients involved approximated 60 to 100 for each group (Figure 4) However for statistical ease the number of subjects for the initial therapeutic trial was projected to 1000 These patients to be considered are all adults with the initial bout of heart failure Regardless of the etiology of their heart disease rhythm—whether normal sinus rhythm or auricular fibrillation presence of heart block degree of edema or severity of the symptom 60% of the patients will have a restoration of their cardiac reserve

Figure 5 demonstrates a typical weight curve of such patients Spontaneous diuresis occurs within twenty four to forty eight hours and thereafter in a step like fashion until the patient becomes edema free This type of curve is indistinguishable from patients who receive digitalis or diuretics

Similarly in Figure 6 a patient with auricular fibrillation treated with bed rest alone will demonstrate spontaneous diuresis and removal of the pulse deficit with improvement of cardiac efficiency It shouldn t be implied that these patients should be

the rule for heart failure The response to therapy is therefore not as dramatic or as satisfactory as the former group It should be noted however that the type of rhythm does not directly play a role in the degree of response Emphasis is on the underlying muscle efficiency and capability of recovery Patients with auricular fibrillation when in stage III respond the same as patients with normal sinus rhythm in this stage of heart disease

Dr Sodeman has brought to our attention and I wish to emphasize the fact that digitalis is only one part of the treatment of heart failure Not only is it necessary to consider the patient as a whole and determine if possible where he stands in relationship to his life span of his disease but also utilize all other therapeutic measures to their maximum Unfortunately there is considerable confusion in the utilization of these therapeutic measures Many of the measures have been advocated for the removal of the edema rather than for improvement in cardiac efficiency Those measures which are palliative and which only treat the peripheral manifestations of congestive heart failure should be recognized and their use limited to the scope of their pharmacologic value Of the various therapeutic measures available only two—bed rest or limited exertion and digitalis restore myocardial efficiency Other measures including mercurial diuretics xanthines carbonic anhydrase inhibitors resins or any method to influence sodium intake or excretion dietary restrictions are all palliative In principle their use as the only form of therapy would be as erroneous as the use of salicylates for the treatment of pneumonia A rational form of therapy demands specific therapy which in this case revolves about measures to improve the cardiac efficiency or attain the maximum restoration of cardiac reserve

I want to demonstrate what is to be expected from various therapeutic measures when used in turn The response of the patient to each measure when used according to optimum effectiveness may thus give us a clue as to prognosis and where the patient stands in the life span of his disease A patient with a good cardiac reserve will respond to those measures influencing muscular efficiency The more advanced patient will require in addition more drastic measures to alleviate the signs and symp

RESPONSE TO DIGITALIZATION

NUMBER OF PATIENTS TO BE TREATED	INCIDENCE OF EFFECTIVENESS	PATIENTS IMPROVED	PATIENTS REQUIRING ADDITIONAL THERAPY
400	80 %	320	80

Figure 7

The effectiveness as noted in Figure 7 is immaterial of the digitalis preparation used or method of digitalization The only prerequisite is the administration of optimum dosage to insure maximum improvement of cardiac efficiency Since an additional 80% of the patients will respond it is possible by the methods which improve cardiac efficiency to improve approximately 90% of patients with their initial bout of congestive heart failure

Of the original group of patients eighty patients remain for further therapy By means of mercurial diuretics which are the most potent of the diuretic agents it is possible to remove the edema and alleviate the symptom in 90% of this group (Figure 8) Again it is necessary to use optimum dosage regardless of mercurial preparation used or method of administration Less than 1% of the patients remain for further therapy related to sodium restriction

The advocates of sodium restriction either by dietary regulation or measures to limit gastrointestinal absorption base their observations upon results performed in chronic disease institutions These patients are the terminal type of patients who have failed to respond to the previous measures and therefore sodium

RESPONSE TO DIURETICS

NUMBER OF PATIENTS TO BE TREATED	INCIDENCE OF EFFECTIVENESS	PATIENTS IMPROVED	PATIENTS REQUIRING ADDITIONAL THERAPY
80	90 %	72	8

Figure 8

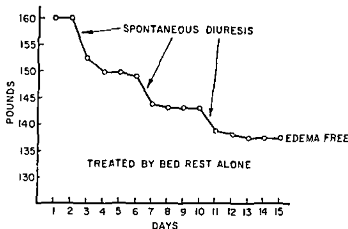


Figure 5

subsequently treated with nothing They should be digitalized because this is the method best suited for improving cardiac efficiency Nevertheless at least we know that in these patients the prognosis is good and that they have a good cardiac reserve Of the original group 600 patients have improved leaving 400 patients for further therapy

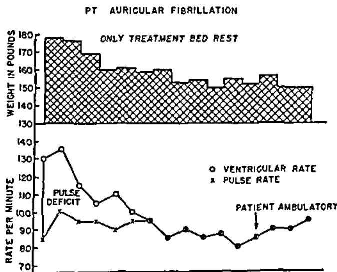


Figure 6

patients beyond the "edema free" state is unphysiologic and might result in electrolyte imbalance.

Since this is a symposium on digitalis I shall concentrate the rest of my remarks entirely upon digitalis.

The schematic figure of the heart structures illustrated in Figure 10 emphasizes the multiple foci that might be influenced by digitalis. The multiplicity of effects might occur simultaneously or each effect might be the only manifestation of digitalis action. From the clinical point of view certain effects overshadow others so that an erroneous impression as to their importance might arise. Thus the effects upon the conducting system or upon rhythmicity might be marked in any particular patient but the effects upon the contractility of the ventricular muscle, the major site of action of digitalis, might be overlooked.

Figure 11 summarizes the known effects of digitalis upon the various cardiac structural sites in man. Note that each site has

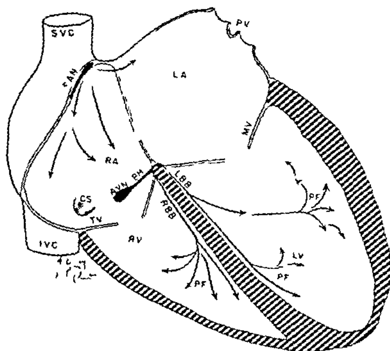


Figure 10

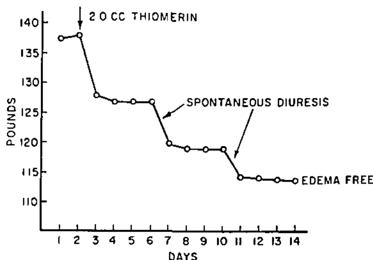
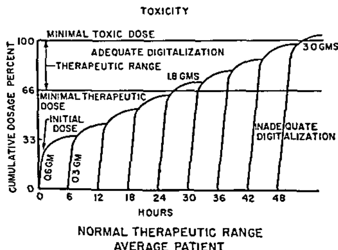


Figure 9

restriction may be essential for control However as a group these patients make up only a small percentage of all patients with diminished cardiac reserve or heart failure It is therefore unwise on the basis of a small segment of patients to advocate as a routine procedure measures which influence sodium intake Since the majority of patients will have restoration of cardiac efficiency by means of proper digitalization the need for sodium restriction is superfluous With restoration of cardiac function the disturbances of kidney function responsible for sodium retention are removed Such a patient could thereafter handle the usual intake of sodium in the same manner as a relatively normal individual A cardiac patient with restored compensation is for all *practical purposes physiologically normal and should not be over* treated by excessive therapeutic regimes

Figure 9 is similar to the one illustrating the effects of bed rest but in this case the results of an administration of a single mercurial diuretic injection Emphasis is upon an edema free" state and not a dry state Every individual cardiac or otherwise will have a diuresis with the administration of potent mercurial diuretics This diuresis reflects a loss of essential interstitial fluid and electrolytes The use of diuretics therefore in cardiac

effect and the minimal dose to achieve toxic manifestations. The larger the therapeutic range or the smaller the therapeutic ratio ($\frac{\text{therapeutic dose}}{\text{toxic dose}} \times 100$) the more desirable the preparation. The factors inherent in the determination of this ratio are too numerous to be discussed here. Suffice it to note that the principles involved hold true for all digitalis preparations. The initial dose of any preparation is based entirely upon predictability data. It represents the largest dose that can be given to the greatest number of patients without the occurrence of any untoward reaction. As a rule it is usually unsatisfactory by itself to produce a therapeutic effect. However, since it is desired to reach this point as quickly and as safely as possible, a large safe initial dose is essential. Subsequent doses are administered at fixed intervals dependent upon the peak of action of each increment, the rapidity of cumulation and rapidity of dissipation. Again these doses are repeated on the sole basis of reaching possibly a desired therapeutic effect without the occurrence of toxicity. Figure 12 thus depicts the course of events noted in the average patient when digitalis leaf is administered with these principles in mind. Any other digitalis preparation utilizing equivalent doses may be substituted. A therapeutic effect is noted only when a sufficient



NORMAL THERAPEUTIC RANGE
AVERAGE PATIENT

Figure 12

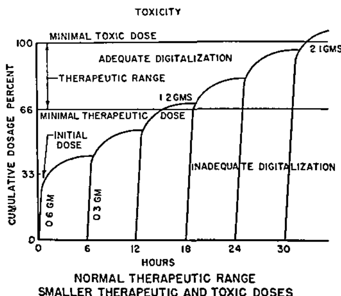
CARDIAC STRUCTURE	RHYTHMICITY	CONDUCTIVITY	IRRITABILITY	CONTRACTILITY
S A NODE	INS GNIFICANT SLOW NG PREDOMNATELY VAGAL		INCREASED WITH TOXIC DOSES TACHYCARDIA	-- --
AUR CULAR MUSCLE		VAGAL INCREASES AT SAME TIME DECREASES REFRACTORY PERIOD MUSCULAR RETARDS CONDUCTIVITY NCREASES REFRACTORY PERIOD	INCREASED WITH TOXIC DOSES PREMATURE SYSTOLES TACHYCARD A C RCUS RHYTHM	INCREASED (EXCEPT IN PRESENCE OF CIRCUS RHYTHMS)
A V NODE	UNKNOWN PROBABLY LOWED	RETARDED VAGAL & MUSCULAR	INCREASED WITH TOXIC DOSES PREMATURE SYSTOLES TACHYCARDIA	–
HIS BUNDLE		RETARDED VAGAL & MUSCULAR	NCREASED WITH TOXIC DOSES PREMATURE SYSTOLES TACHYCARDIA	
PURKINJE FIBERS		UN OWN	NCREASED W TH TOXIC DOSES PREMATURE SYSTOLES TACHYCARDIA	
VENTRICULAR MUSCLE		RET RDS	DECREASED THERAPEUTIC DOSES INCREA ED TOXIC DOSES	NCREASED

Figure 11

four basic physiologic functions However dependent upon the specialization of the particular heart muscle site certain functions would be more manifest than others for example conduction for the bundle of His or contractility for the ventricular muscle Furthermore certain functions as indicated might be influenced by vagal action in addition to a direct muscular effect In any particular patient the multiplicity of effects that might occur from the action of digitalis upon any of the above sites thus results in a complex over all response The most important effect that upon the contractility of the ventricle is often overlooked or over shadowed by the effects upon heart rate or conductivity The latter effects are secondary and should not detract from the main action of digitalis—the ability to improve the efficiency of cardiac work by direct action upon muscular contractility

Digitalization of a patient is a twofold problem First there is the problem of initial digitalization and second the maintenance of the effects achieved with the initial digitalization Figure 12 depicts the principles involved with initial digitalization The purpose is to achieve restoration of myocardial efficiency as quickly and as safely as possible To accomplish this it is necessary to give sufficient digitalis to achieve an adequate therapeutic effect As with all drugs useful in medicine there exists a therapeutic range which reflects the difference between the minimal dose required to institute a desired therapeutic

urginin maritima urginin indica and digilanid The only exception has been amorphous gitalin which possesses a greater range Second it is immaterial what the initial and subsequent doses are digitalization can never be achieved until the optimum therapeutic dose is reached Larger doses might reach this dose sooner but overshooting of cumulative effects might result in toxicity Cumulation of small increments to avoid this phenomenon is recommended Third it is impossible from the appearance of the patient the physical examination or the severity of the subjective complaints to predict in advance what dose of any digitalis preparation will be required to produce an optimum therapeutic effect Digitalization for each patient is a trial and error procedure Reliance upon any fixed dose or administration of a single dose will result in inadequate digitalization in the majority of patients With a large series of patients it is possible to establish a distribution curve which will indicate what dose will digitalize the greatest number of patents This dosage however is not applicable to patients to the right or left of this point upon the distribution curve The only rule is the administration of sufficient dosage



NORMAL THERAPEUTIC RANGE
SMALLER THERAPEUTIC AND TOXIC DOSES

Figure 14

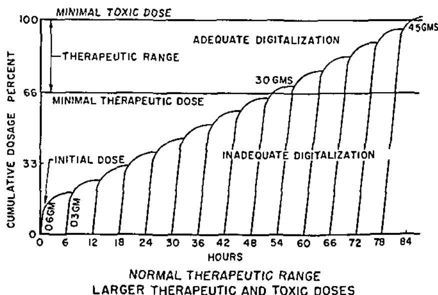


Figure 13

amount of digitalis has accumulated If edema is present this is manifested in the patient by the onset of diuresis In other words when the optimum dosage has been reached the restoration of cardiac efficiency reverses the disturbances in kidney function and urine flow becomes normal Any other effect upon cardiac function such as change in heart rate conduction or electrocardiogram are secondary and might not reflect improvement in the work capacity of the heart muscle

When the desired therapeutic effect is achieved cumulative repetitive doses are no longer necessary The second problem of digitalization—that of maintenance of desired therapeutic effects takes over However for purposes of research to determine the therapeutic range let us continue the administration of the digitalis preparation at six hour intervals until minor signs or symtoms of toxicity occur Several facts become apparent The usual patient with the initial bout of congestive heart failure required approximately 66% of the toxic dose of digitalis leaf before an adequate therapeutic effect is achieved *This small therapeutic range* has also been noted for digitoxin digoxin lanatoside C ouabain

to diminish until it is abolished completely Several clinical possibilities for digitalization thus exist As noted in Figure 15 there is a narrower therapeutic range at the expense of a smaller toxic dose In this case the therapeutic dose is average but toxicity is noted with dosages used at the next dose administration

In Figure 16 the toxic dose remains average but the therapeutic dose is just short of the toxic level

In Figure 17 both therapeutic and toxic doses are elevated but the patient manifests a narrow therapeutic range In some patients the therapeutic range might be so narrow that overshooting of the therapeutic level into the toxic effects occurs when the dose increment might be too large This is seen in Figure 18

Such a patient usually reveals a therapeutic response in reverse when the toxic manifestations subside upon discontinuation of the drug

The foregoing illustrations are indicative for the need to obtain an optimum dosage for each patient

Figure 19 reveals that the method of digitalization the size of the individual dose and the factor of dissipation are not sig

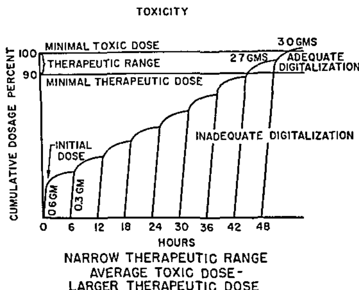


Figure 16

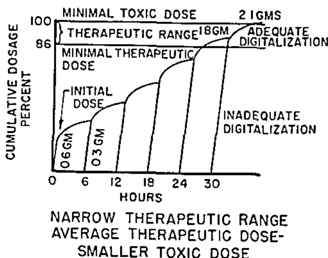


Figure 15

regardless of the average or mean dose until a desired therapeutic effect is achieved or toxicity occurs Fourth the determination of the therapeutic range in any individual patient reflects to some degree the cardiac reserve The fact that myocardial efficiency can be restored is indicative that a therapeutic range exists In the usual patient with the first bout of failure utilizing all digitalis preparations with exception of amorphous gitalin the therapeutic range approximates one third of the toxic dose Figure 12 indicates this phenomenon as noted with average therapeutic and toxic doses However it is possible for patients to possess a normal therapeutic range with different dosage possibilities

In Figure 13 the minimal therapeutic dose is similar to the toxic dose noted previously However, in spite of this the usual therapeutic range is present Such a patient emphasizes again the necessity for individualizing therapy Cessation of multiple dose administration when the average dose had been reached would never have resulted in digitalization

Figure 14 represents the reverse possibility where therapeutic and toxic doses are smaller than average but the therapeutic range is maintained

With advancing heart disease the therapeutic range is found

nificant in terms of the amount of digitalis preparation required for therapeutic or toxic effects With digitoxin the average therapeutic and toxic doses were identical if one started digitalization with 0 6 mg and repeated 0 3 mg every six hours or start with 1 2 mg wait twenty four hours and then administer 0 3 mg every six hours The Gold method of digitalization in the majority of patients was thus found to be inadequate The same average or toxic therapeutic doses were also noted for digitoxin if the preparation was given every six hours or daily In the latter case it took longer to cumulate sufficient digitoxin for a therapeutic or toxic effect but the dosage by both methods was similar Surprisingly the same toxic dose was noted for digoxin when this was determined by repeated six hour dosage or daily administration Apparently the factor of dissipation does not enter into the problem of initial digitalization as long as each increment of dosage administration is large enough to result in cumulation Experiences with amorphous gitalin and digilanid were similar

The question has been raised as to the purity of gitalin As is well known this preparation is a mixture of glycosides It consists primarily of water soluble components However in the process of preparation two alcoholic soluble components of leaf namely digitoxin and gitoxin are carried over in the extract In any case the content of digitoxin is never higher than 10% and

METHOD OF DIGITALIZATION

DIGITALIS PREPARATION	MULTIPLE DOSES DAILY: AVERAGE THERAPEUTIC DOSE	MULTIPLE DOSES DAILY: AVERAGE TOXIC DOSE	DAILY DOSE (UNDIVIDED): AVERAGE THERAPEUTIC DOSE	DAILY DOSE (UNDIVIDED): AVERAGE TOXIC DOSE
DIGITOXIN	(1) 2 2 MG (2) 1 6 MG (3)° 2.2 MG	4 1 MG 4 6 MG	1 7 MG	3 8 MG
DIGOXIN	3 75 MG	6 0 MG		5 9 MG
GITALIN (AMORPHOUS)	5 6 MG	15 1 MG	6 0 MG	
DIGILANID	6 6 MG	10 03 MG	6 4 MG	8 65 MG

DOSE ADMINISTERED EVERY 6 HOURS

° INITIAL DOSE 1.2 MG FOLLOWED 24 HOURS LATER BY 0 3 MG EVERY 6 HOURS

Figure 19

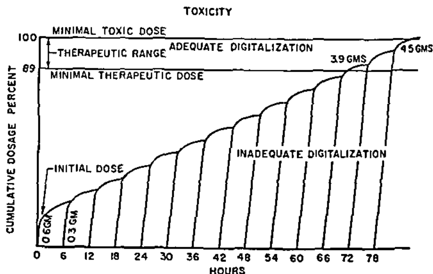


Figure 17

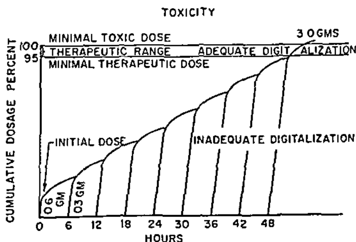


Figure 18

is a tachycardia and treatment would be inadequate if their normal basic bradycardia was not restored

These remarks supplement the basic conclusion that the slowing of the heart rate in patients undergoing digitalization is secondary to increased myocardial efficiency and not per se responsible for improvement of cardiac compensation Evidence for this conclusion takes several forms Improvement may be noted before the heart rate is appreciably slowed This is noted first of all in patients with normal sinus rhythm who restore compensation without significant change in heart rate Secondly patients with auricular fibrillation when given digitalis and atropine simultaneously will present the expected compensation in the usual time without affecting the ventricular rate until the direct muscular action of digitalis becomes dominant Thirdly a rare patient with auricular fibrillation will have complete restoration of compensation without altering the tachycardia Further evidence is available in that patients with auricular fibrillation when treated by bed rest alone will have compensation restored similarly to patients with normal sinus rhythm The ventricular rate will slow of its own accord as compensation is achieved Finally rapid auricular fibrillation in the absence of myocardial failure is not slowed by digitalis unless toxic doses are used

Utilization of the electrocardiogram as the endpoint for digitalization is fraught with many objections Advocates of this procedure base their conclusions upon effects noted in a highly select group of sensitive subjects chosen from many hundreds of patients The fact that selection of these subjects has removed many variables existent in clinical medicine and which are probably more significant for the patients over all response to therapy has been completely ignored The changes in the ST and T waves of the electrocardiogram noted with certain glycosides does not mean that this phenomenon occurs for all glycosides and therefore applicable as a guide of therapy

Figure 20 indicates that with digoxin the electrocardiogram might be unaltered in some patients even though an optimum therapeutic effect and toxicity occurred Similar results have been noted with lanatoside C ouabain and have been also noted many times with digitalis leaf or digitoxin The absence of electro

gitoxin is inert by gastrointestinal administration The problem then revolves whether this amount of digitoxin contributes to the gitalin effects There are several objections to this thesis First of all the clinical effects noted with gitalin in terms of therapeutic range can not in my experience be duplicated by digitoxin Second an opportunity arose to evaluate a highly purified water extract of digitalis leaf which was completely free of digitoxin This preparation although still a mixture of water soluble glycosides also possessed a greater therapeutic range The only difference was the smaller dose required by the purified preparation over the usually available amorphous commercial gitalin In all the respects the properties were the same

It is my contention that the end point for adequate digitalization is the restoration of myocardial efficiency to the level it *existed prior to the occurrence of the congestive heart failure* This efficiency *is a manifestation of heart muscle contractility* and not the changes noted in heart rate In the past too much emphasis has been placed upon the use of the heart rate for the determination of the optimum dose It is the practice by many to continue digitalization until the heart rate is between 70 and 80 beats per minute and then attempt to maintain this rate by a daily dose of some digitalis preparation No account is taken that many patients with this heart rate are still in severe heart failure because the heart muscle is still inefficient Utilization of the heart rate between 70 and 80 is based upon a mistaken interpretation of its significance for cardiac patients It must be emphasized that criteria for the normal heart rate from 60 to 100 is based entirely upon normal relatively young adults No cognizance is taken of the fact that a rate of 60 or 70 might be a tachycardia *for a patient with heart disease Since there exists some* correlation between the size of the heart and the optimum heart rate for efficiency it is evident that a large heart as noted with congestive heart failure would be more efficient with a rate slower than would be anticipated for the normal criteria Secondly many elderly patients possess a relatively bradycardia merely as a reflection of slowing of bodily processes With decompensation these patients might elevate their heart rate to 70 or 80 which ordinarily would not be considered significant However in these patients it

on a small daily dose equivalent to an accepted maintenance dose of any digitalis preparation and the physician assumes that sufficient cumulation will occur to result in digitalization Our studies indicate that it is impossible to digitalize any patient with a maintenance dose of any digitalis preparation If subjects who have been well maintained by a small daily dose are allowed to relapse in failure by discontinuing their glycoside such subjects will never compensate by restoring the same daily dose which pre viously was adequate for maintenance At least two or three times the patients subsequent minimal daily maintenance dose is re quired for initial digitalization The practice of advising 0 1 mg of digitoxin or 0 1 gm (1½ grains) of digitalis leaf daily as the digitalizing procedure should be discouraged

Figure 21 schematically presents the course of events noted with maintenance digitalis therapy By definition a maintenance dose is that required to be administered at periodic intervals preferably daily in order to maintain the effects achieved with initial digitalization Evidence will be presented later that it is not the amount of digitalis preparation required by daily ad ministration to restore the amount eliminated A misinterpreta tion of available facts has unfortunately beclouded the issue and has detracted from the fundamental concept pertaining to achieved myocardial effect namely maintenance of restored cardiac muscle efficiency Adequate maintenance then is the con tinuation of the digitalis effect within the therapeutic range of the individual If the maintenance dose be discontinued the desired effect subsides at a rate dependent upon numerous variables The

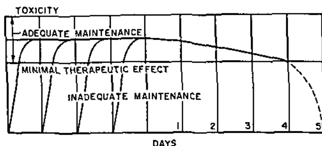
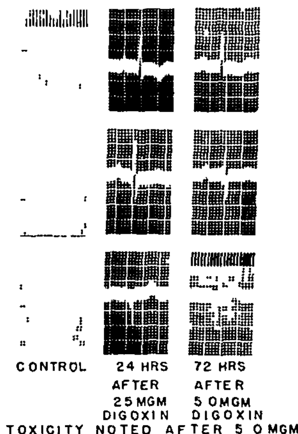


Figure 21



PATIENT C L AGE 63
CARDIAC DIAGNOSIS
A ARTERIOSCLEROSIS
B CORONARY SCLEROSIS MYOCARDIAL FIBROSIS
C REGULAR SINUS RHYTHM ANGINAL SYNDROME

Figure 20

cardiographic effects does not mean that a therapeutic effect or toxicity has not occurred Conversely marked electrocardiographic changes might occur with a dose of any digitalis preparation far short of the therapeutic or toxic doses

Before considering the problems of maintenance I would like to briefly discuss a method of digitalization which is used extensively and which I believe is inadequate A patient is often started

25% chance that satisfactory maintenance is achieved and a 5% chance that toxicity might occur With 0 1 gm the likelihood of achieving maintenance is 65% while that of toxicity rises to 10% With higher doses it will be noted that when 0 2 gm of leaf is administered daily the likelihood of achieving maintenance or toxicity is equally good In other words the best choice of a maintenance dose when it is known that initial digitalization is satisfactory is the 0 1 gm dose This dosage level allows the great est range However there are certain features in choice of main tenance dosage which must be emphasized First as in the case of initial digitalization maintenance therapy is also a trial and error procedure Every patient should be considered as an indi vidual experiment No dosage scheme can predict in advance what dosage will be satisfactory for any patient Predictability figures are of help in choice of dosage but this dosage might re quire adjustment for maximum effectiveness Second there is a rough correlation between the total dosage required for initial digitalization and the size of the daily dose for maintenance Third failure to recognize the fact that certain patients require large daily doses for maintenance has resulted in unsatisfactory therapy and continuation unnecessarily of chronic congestive heart failure Patients have been observed who require as much as 0 7 to 1 0 gm of digitalis leaf or equivalent amounts of gly

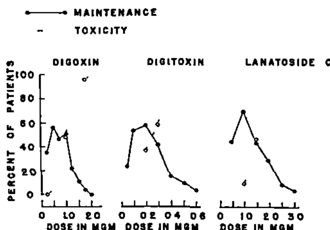


Figure 23

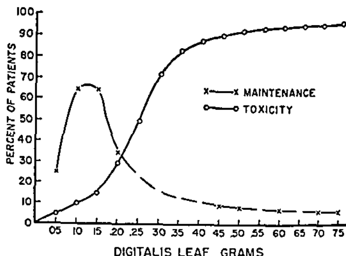


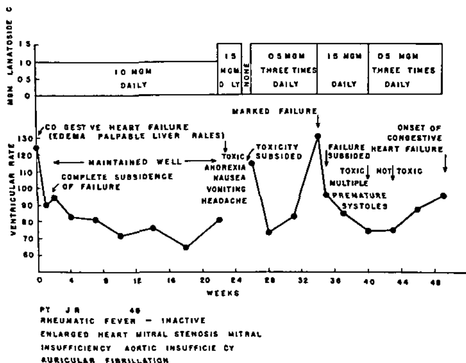
Figure 22

most important variables are the severity of the underlying heart disease and the type of cardiac glycoside used The more advanced the heart disease the more rapid the rate of dissipation of effect Even digitoxin or digitalis leaf might lose all their effects within twenty four hours in the advanced cardiac patient In the usual patient however the rapidity of dissipation of effect of each particular glycoside will determine the duration of maintenance effect As illustrated in Figure 21 digoxin was the glycoside used When it was discontinued congestive heart failure recurred in 5 days It is of interest to note that the rapidity of dissipation of effect is the same whether the patient has been observed immediately after initial digitalization or whether the patient has been on maintenance therapy for weeks or months Maintenance of effect does not alter the rapidity with which the effect might subside if therapy is discontinued

Figure 22 presents a predictability curve applicable for all cardiac preparations It permits an understanding of what is to be expected when any dose level is administered for maintenance therapy Substitution of equivalent dosages for other cardiac glycosides in place of those designated for digitalis leaf as noted in Figure 23 indicate the usefulness of this type of curve With the daily administration of 0 05 gm of digitalis leaf there is a

strated that the practice of dividing the total daily dose particularly of rapidly dissipated glycosides such as digoxin or lanatoside C will result in poor maintenance or failure An undivided dose as a single daily dose is always the most satisfactory way of administering these preparations The effects of each increment of total dosage when given divided is never sufficient for cumulation and maintenance

Figure 27 summarizes the pertinent information in regard to four digitalis glycosides There are certain features that must be kept in mind in the choice of any preparation The dosage for each glycoside has to be determined in its own right There isn t any correlation between their digitalis or cat unitage and the



NOTE TOXICITY WITH UNDIVIDED DAILY DOSE OF 1 5 MGM AND LOSS OF TOXICITY WITH SUBSEQUENT FAILURE WHEN TOTAL DOSE WAS DIVIDED

Figure 26

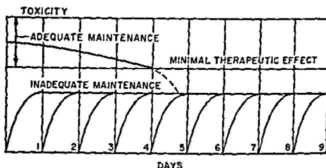


Figure 24

cosides for adequate maintenance Fourth as noted in Figure 24 continuation of an inadequate daily dosage of a digitalis preparation following satisfactory initial digitalization will result in a return of congestive heart failure A daily dose of a digitalis preparation does not mean maintenance unless with that dosage it is possible to maintain satisfactory cardiac function This is further emphasized in Figures 25 and 26 wherein it is demon

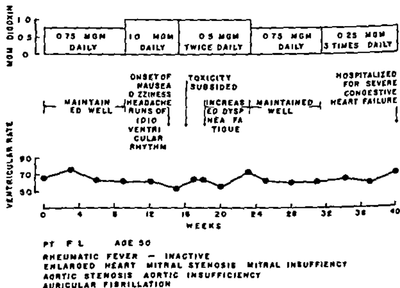


Figure 25

The possible advantages of glycosides over digitalis leaf have been over emphasized and perhaps distorted The glycosides can not result in a greater myocardial efficiency than can be produced by digitalis leaf This observation however must be modified to account for possible effectiveness of amorphous gitalin over other cardiac preparations on the basis of a greater therapeutic range This property does not mean that greater heart efficiency occurs It merely reflects the possible restoration of an effect which would be produced by the other glycosides if toxicity was not a factor In other words in the usual patients who still maintains a therapeutic range no matter how narrow all digitalis preparations in equivalent dosages are equally effective

It has been claimed that certain glycosides have less irritability upon the heart and might be even safer to use Evidence to satisfy such claims hold true only if the digitalis preparation possesses a greater therapeutic range The administration of all preparations to the point of toxicity will result in almost identical manifestations of toxicity both qualitatively and quantitatively The greater therapeutic range might play a role in that a larger dose may be necessary to result in toxicity but the type and severity of the toxicity will be identical A patient who presents multiple ventricular beats with coupling to digitalis leaf will also present the same irritability to any digitalis preparation with the same narrow therapeutic range In our experience it is not unusual for a patient to present the same symptom complex of toxicity to any digitalis preparation Exceptions of course occur but it could be predicted that the same pattern of toxic manifestation will recur with subsequent episodes of toxicity

The importance of completeness of absorption has been exaggerated As long as absorption is predictable it is immaterial whether it is 5% or 100% Digitalization in either case was equally satisfactory for both initial effects and maintenance

Rapidity of action plays a role for parenteral administration but this property is not evident when the preparations are studied for oral administration Attainment of the optimum dose during initial digitalization will occur in approximately the same time for all preparations as long as equivalent dosages are used

The occurrence of gastrointestinal irritation to digitalis leaf

COMPARATIVE SUMMARY OF THE AMBULATORY USE OF DIGOXIN DIGITOXIN LANATOSIDE C AND GITALIN (AMORPHOUS)

	DIGOXIN	DIGITOXIN	LANATOSIDE C	GITALIN
DAILY UNDIVIDED DOSE MOST LIKELY RESULTING IN MAINTENANCE	0.5 MG	0 1 MG	1 0 MG.	0 5 MG
DAILY UNDIVIDED DOSE MOST LIKELY RESULTING IN TOXICITY	1.0 MG	0 2 0.3 MG.	1.5 2.0 MG.	1 0 MG
PATIENTS PRESENTING TOXICITY ON DOUBLING MINIMAL MAINTENANCE DOSE	63 6 %	65 4 %	62 9 %	41 0 %
NUMBER OF TRIALS RESULTING IN POOR MAINTENANCE REGARDLESS OF DOSE	12 6 %	10 7 %	21 %	12 6 %
EASE OF ACHIEVING MAINTENANCE	GOOD	GOOD	FAIR	GOOD
EASE OF PREDICTING DOSE	GOOD	GOOD	TRIAL & ERROR	GOOD
DISSIPATION	RAPID	SLOW	RAPID	MODERATE
DURATION OF TOXICITY	SHORT	LONG	SHORT	SHORT

Figure 27

actual amount required for initial digitalization maintenance or toxicity One unit of digitoxin is not interchangeable for any other preparation for equivalent effects

The problem of standardization of digitalis preparations is related primarily to the treatment of the ambulant or maintenance patient Once an effect has been obtained it is essential that the patient be continued in this state without fluctuation of potency The problems inherent in the potency of digitalis preparations are not of major significance for initial digitalization According to previously discussed concepts digitalization can be obtained with any digitalis preparation administered orally as long as some absorption occurs Since the desired action is obtained by a trial and error procedure the total dose in terms of patient to patient may vary widely What is important however, is that a particular digitalis preparation used in any specific patient should possess a uniform potency from lot to lot to avoid fluctuations in degree of maintenance of digitalization Methods of standardization have not been entirely satisfactory in assuring uniformity from lot to lot Digitalis leaf preparations might possess the same digitalis unit for the cat but might differ widely in potency when used in man It is for this reason that the glycosides have achieved the greatest popularity Although standardization is still required uniformity from lot to lot can be assured

The possible advantages of glycosides over digitalis leaf have been over emphasized and perhaps distorted The glycosides can not result in a greater myocardial efficiency than can be produced by digitalis leaf This observation however must be modified to account for possible effectiveness of amorphous gitalin over other cardiac preparations on the basis of a greater therapeutic range This property does not mean that greater heart efficiency occurs It merely reflects the possible restoration of an effect which would be produced by the other glycosides if toxicity was not a factor In other words in the usual patients who still maintains a therapeutic range no matter how narrow all digitalis preparations in equivalent dosages are equally effective

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The importance of completeness of absorption has been exaggerated As long as absorption is predictable it is immaterial whether it is 5% or 100% Digitalization in either case was equally satisfactory for both initial effects and maintenance

Rapidity of action plays a role for parenteral administration but this property is not evident when the preparations are studied for oral administration Attainment of the optimum dose during initial digitalization will occur in approximately the same time for all preparations as long as equivalent dosages are used

The occurrence of gastrointestinal irritation to digitalis leaf

has also been exaggerated One must differentiate the gastro intestinal symptoms of true central toxicity to actual local irrita tion The latter is only a problem in initial digitalization if the priming dose is excessive The likelihood of gastro intestinal ir ritation is small with the usual small doses used for this purpose It is a rare patient who cannot tolerate digitalis leaf as a mainte nance preparation The patient who presents intolerance to digi talis leaf usually does so because of true toxicity The rare patient manifesting diarrhea to digitalis leaf might be free of this disturb ance with a glycoside However the administration of equivalent doses of any digitalis preparation with the same therapeutic range as digitalis leaf will also result in gastrointestinal intolerance

Rapidity of dissipation however is of some significance Not only must it be taken into account for proper adjustment of main tenance dose but this property serves a useful purpose in some patients Toxic manifestations with their use are short lived and in this respect these properties offer some advantage for the ad vanced heart patient where toxicity might occur readily

The duration of action of digitalis has been the subject of numerous investigations It is unfortunate that chemical methods have not been satisfactory for a complete analysis of the problem It therefore becomes necessary to rely upon the effects that can be observed after a full dose of any digitalis preparation Any end point might be used It is possible to follow the duration of digitalis action upon (1) ventricular rate of patients with auricu lar fibrillation (2) changes in the ST segment T wave Q T interval and PR interval of the electrocardiogram (3) persist ence of improved myocardial efficiency in terms of control of signs and symptoms of congestive heart failure (4) persistence of changes in cardio dynamics and (5) persistence of signs and symptoms of toxic manifestations It is at once apparent that the persistence of action of any digitalis preparation upon any of the above is an individual phenomenon and might have no relation ship to each other Conclusions based on one type of study can not be carried over to another Such studies might reveal me chanisms of digitalis action but the information so gained might not reflect the clinical utilization for the major problem—treatment of congestive heart failure Every effect noted with digitalis has its own rate of dissipation

Figure 28 illustrates the persistence of action upon the ventricular rate of patients with auricular fibrillation following a full toxic dose of various digitalis preparations The number of days required for loss of effect as illustrated for each preparation is an average figure For example ouabain possesses an average duration of four days However this might vary between one day to twelve days There is considerable overlapping of each preparation Even digitoxin and digitalis leaf which possess the longest duration of action might in patients with advanced heart disease lose the effect upon the ventricular rate within twenty four hours It thus becomes necessary to re evaluate our concepts as to duration of effect Is it the digitalis preparation or the capacity of the heart muscle to present a specific effect? Since we are concerned clinically with only one factor—the effect that is produced then it is immaterial what digitalis preparation is used Properties of absorption dissipation and dosages required are immaterial except as they relate to production of and maintenance of desired effect

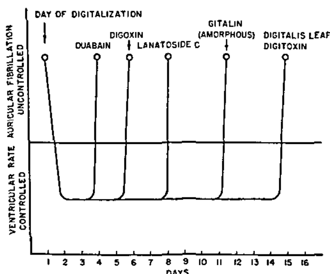


Figure 28 Schematic representation of persistence of digitalis effect upon the ventricular rate of patients with auricular fibrillation following full digitalization and subsequent discontinuation of therapy

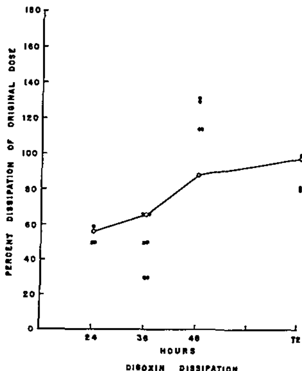


Figure 29 At definite intervals following initial digitalization groups of patients are redigitalized until the same response (minimal signs and symptoms of toxicity) is attained The amount required for the second digitalization indicates the rapidity of dissipation of a full digitalizing dose in terms of toxic effect

If we for the moment ignore the dissipation of effect and evaluate the problem in terms of actual dosage required to replace *the amount eliminated or destroyed daily in the body* we note several features of interest Although the usual patient requires four days to lose the effect from ouabain that patient can be given a full dose of ouabain twenty four hours after initial digitalization Apparently the effect outlasts the amount of drug within the body or heart muscle

Studies with digoxin Figure 29 illustrate the same phenomenon Within forty eight to seventy two hours the average patient could tolerate a full dose of digoxin after initial digitalization to the point of toxicity with digoxin and yet the effects of

this glycoside upon the ventricular rate of patients with auricular fibrillation might last for six days Similar studies still uncompleted indicate the same phenomenon with lanatoside C As will be indicated later digitalis leaf and presumably digitoxin also possess the same properties These studies are indicative of only one interpretation The effects produced by digitalis glycosides persist beyond the total elimination dissipation or destruction from the body or heart muscle This is particularly so for the effects associated with myocardial efficiency Restoration of compensation especially if the precipitating factor for the failure has been removed often persists for many weeks or months a period far beyond the anticipated pharmacologic effects of digitalis

More recent studies throw light upon this problem which may have practical significance These studies date back to 1940 at which time Drs De Graff Rose and I described a method of digitalization utilizing a combination of ouabain and digitalis leaf The theory for this method is illustrated schematically in Figure 30 It consisted briefly of the initiation of digitalization with 0 5

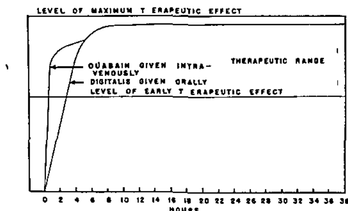


Figure 30 Schematic representation of absorption and cumulation following combined therapy of simultaneous administration of ouabain intravenously and digitalis orally Principle To initiate digitalization by safe dose of rapidly acting rapidly dissipated parenteral glycoside and to supplement and maintain the effects produced by the simultaneous administration of an oral digitalis preparation

mg of ouabain and by simultaneous administration of digitalis leaf achieve complete digitalization within a period of six hours We were able within twenty four hours to begin maintenance therapy with the usual daily dose The method itself is of no consequence What however is significant is that a small daily dose of digitalis leaf was capable of maintaining the improved cardiac efficiency Initial digitalization was achieved with a very rapidly dissipating glycoside and the amount of digitalis leaf administered simultaneously was below that expected to be effective According to all known concepts a patient digitalized in this manner should promptly go back into decompensation in spite of a subsequent small dose of digitalis This did not occur Several possible explanations were considered Did the combination of digitalis leaf offset the rapid dissipation of ouabain? This was tested by administering digitalis leaf to the point of toxicity twenty four hours after initial digitalization The patients took on the average a total dose of digitalis leaf as if no previous ouabain had been administered In other words ouabain had been eliminated but the difference in total toxic dose was the amount of digitalis leaf administered initially with the ouabain The second possibility was that instead of glycoside dissipation the effect achieved was of significance If full compensation was achieved regardless of glycoside then it was possible to maintain this effect without redigitalization of the patient This was tested as follows Patients were digitalized to toxicity by ouabain utilizing the Wycoff Goldring method Twenty four hours later instead of redigitalizing the patient as has been recommended the patient was placed on a predicted maintenance dose of digitalis leaf These patients maintained their efficient cardiac status in spite of the rapid dissipation of ouabain Similar results were obtained with lanatoside C and digoxin It thus became evident that a patient digitalized by a rapidly dissipated glycoside need not be re digitalized the next day As long as the cardiac function has been restored a daily small maintenance dose is all that is necessary thereafter The only exception is the far advanced cardiac who dissipates the effects of any digitalis preparation rapidly Unless an optimum initial dose was administered the daily maintenance dose might be difficult to establish

All evidence so far suggested that the effect is more important than the glycoside or dosage. Studies with digitalis leaf further emphasized this concept. Preliminary studies upon the therapeutic range of digitalis leaf were carried out upon ambulatory patients. Patients who were well maintained with a daily dose of digitalis leaf were chosen. All patients, if digitalis was discontinued, lapsed into failure. When compensation was maintained the patients were given an additional dose of digitalis leaf before returning to clinic. The first dose consisted of 0.1 gm in addition to the maintenance dose. Three weeks later the dose consisted of 0.2 mg. At intervals of three weeks the patients were given increasing doses of digitalis leaf. When 0.8 gm. of digitalis was administered to this group of patients without the occurrence of toxicity, it was therefore advisable to discontinue the study in ambulatory patients and proceed in hospitalized patients. This study, however, revealed that patients on a daily dose of digitalis leaf might take a large single additional dose without danger of toxicity. It confirmed that patients well maintained possess a good therapeutic range. Further confirmation was attained in the hospitalized group of patients. For this purpose any hospitalized patient with congestive heart failure was utilized. The only prerequisite was that these patients be on a daily dose of digitalis leaf. These patients varied in the severity of their heart disease. The majority were well maintained with a small daily dose while others required frequent injections of mercurial diuretics to be edema free. Titration of the therapeutic range was accomplished in each case by administration of a small dose of digitalis at six hour intervals until minor signs and symptoms of toxicity occurred. This procedure was carried out regardless of the previous history of digitalization and the amount of digitalis taken daily. On the basis of re-digitalization the patients separated themselves easily into several groups. The first group took a dose of digitalis as if no previous digitalis had been administered and as if they were not on a maintenance dose. Those patients were considered "early" in their heart disease and did not require diuretics. The second group required a smaller total dose than the average for initial digitalization but also required no mercurial diuretics. These patients were considered to be further along in their heart

disease but maintenance was still possible The other patients were all receiving frequent mercurials and grouped themselves into two categories The majority upon redigitalization" had restoration of cardiac reserve and lost all signs and symptoms of congestive heart failure Their previous daily dose of digitalis was therefore inadequate However upon re digitalization the same daily dose or adjustment of daily dosage was adequate for maintenance The minority was unable to tolerate any significant further administration of digitalis and became toxic usually before an additional 0 5 gm of digitalis was administered These patients had exhausted their therapeutic range and were no longer responsive to digitalis and therefore required supplementary *measures such as diuretics*

Of greatest significance was the first group of patients Here were patients who were well maintained and presumably each daily dose of digitalis restored the amount that was eliminated If this was so then the daily dose should have maintained a high level of digitalis within the body and any further digitalis dosage would have resulted in immediate toxicity Obviously a daily dose does not restore the amount of digitalis eliminated daily Since such patients could tolerate a full dose of digitalis upon titration an alternate explanation would be that the daily dose maintains the effects achieved with initial digitalization and the amount eliminated is of no significance as long as the effects are maintained Emphasis is again upon effect and not upon digitalis preparation or dosage

Further proof was forthcoming when one determines at what point after initial digitalization is it possible for the patient to take a full dose of digitalis upon re digitalization Preliminary studies indicate that if no digitalis is administered as a daily dose after initial digitalization then approximately seven days must elapse before a full re digitalizing dose is possible This is in contrast to the classical studies of Pardee who however carried out the experiments for only seventy two hours A patient therefore does not eliminate 1½ grains of digitalis leaf daily as he concluded If the patient is placed upon a daily maintenance after initial digitalization preliminary studies again reveal that re digitalization to full dosage might be seen in some patients as early as three to four weeks

Recent studies with isotopes are misleading Measurements of radio activity do not reflect total glycoside dissipation The metabolism of the glycoside allows the radio active component to participate in other metabolic processes of the body Its determination and final dissipation weeks after administration does not mean that the glycoside is slowly dissipated As noted the greatest portion of the radioactivity is eliminated in forty eight hours evidence again reflecting the rapidity of elimination of the glycoside What could not be measured by isotope studies is the persistence of pharmacologic effects which are longer in duration than the presence of the glycoside within the body

These studies on re digitalization allow a schematic presentation of the course of events noted in the usual patient in regard to therapeutic range and maintenance of cardiac efficiency

As noted in Figure 31 early in the heart disease the range is large and the patient is maintained with a daily dose of any digitalis preparation without sign or symptom of congestive heart failure As long as a therapeutic range exists it is not necessary to treat the patient with any other form of therapy than an adequate maintenance dose of some digitalis preparation At some point in the patient s cardiac status it will be noted that the daily maintenance dose has become a toxic dose The therapeutic range has been obliterated At this point our concepts of daily digitalis dosage require alteration Maintenance of improved cardiac efficiency is no longer possible since toxicity occurs with the necessary dose A daily dose is required but it is not a maintenance dose It is a maximum tolerated dose It is at this point of obliteration of the therapeutic range that diuretics are necessary to supplement digitalis therapy

The course of events illustrated in Figure 31 are noted with

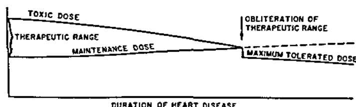


Figure 31

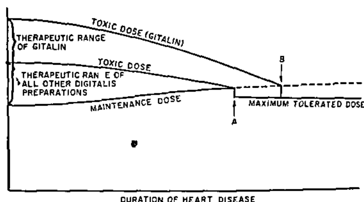


Figure 32

all digitalis preparations possessing the same narrow therapeutic range discussed earlier The only exception in my experience has been amorphous gitalin However even with this preparation the principles are the same as noted in Figure 32 but somewhat delayed in duration Thus many patients who have stopped responding to digitoxin digitalis leaf etc because of toxicity might respond to gitalin in equivalent dosages because of the greater range with this preparation

These studies reveal some practical points The prime action of digitalis is restoration of myocardial efficiency An optimum dosage is required for each patient which could only be determined individually If the patient is receiving a digitalis preparation and signs and symptoms of congestive heart failure are present the only possible conclusion is that the dosage of the digitalis preparation is inadequate Three possibilities exist First the patient never received an optimum initial digitalization The daily dose was therefore not a maintenance dose A patient might have been adequately digitalized initially but the daily dose as noted in Figure 24 was insufficient for maintenance Second the patient might have been given too large a daily dose which because of toxicity has depressed optimum cardiac efficiency Third the patient has advanced heart disease and a maintenance dose is impossible because of obliteration of the therapeutic range In the case of the second possibility discontinuation of the digitalis and adjustment of dosage is all that is necessary However for

the other two possibilities only careful titration of the patient with a digitalis preparation could disclose the facts Such a determination of the therapeutic range offers a guide not only to prognosis but also a practical means of determining the optimum effects of digitalization

These concepts emphasize the teachings of Withering Digitalis or any cardiac glycoside should be given until a desired effect is achieved or minor signs or symptoms of toxicity occur This is the therapeutic range Every patient is a law unto himself It is immaterial which preparation or method of digitalization is utilized as long as the patient is evaluated on his own rights and principles inherent in all therapeutic procedures followed

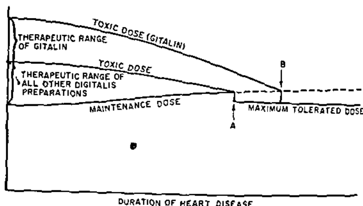


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Active therapy with digitalis represents our major problem What happens with prophylactic use of this drug is a matter I think that is becoming a little more of concern to some of us than it has in the past Generally speaking with preparations that we have and with the watching of our patients we have not given this drug to patients prophylactically before surgery and until there is a definite clinical indication for it There are times when the drug is useful in a patient having recurrent disease and I suppose that you may call that a prophylactic use In widely spaced episodes of fluttering for example where patients develop remarkable symptoms when they go into paroxysms the drug can be used to control ventricular rate when it is not or does not seem plausible from the timing of these episodes and so on to keep a patient on quinidine for a long period of time However in surgery at the present time there are some areas where the prophylactic use of the drug has been used and is indicated In the latest Stanford series of patients who have been subjected to mitral surgery there is a very high incidence of paroxysmal auricular fibrillation and when the frequency of those attacks becomes great enough in a group it might be desirable to digitalize a patient preoperatively But you see that is a rather specific unusual indication as far as the prophylactic use of this drug is concerned In large part in the practices of most of us I believe prophylactic use has very little place

Uncontrolled atrial fibrillation and flutter are problems that are very important clinically The same is true of paroxysmal tachycardia I will bypass these problems for I know that Dr Lown is discussing them

If one encounters paroxysmal auricular tachycardia that he cannot stop he becomes concerned about the use and sequence of procedures from pressing on the eyeball or the cartoid sinus or through the use of mecholyl emetics and digitalis I am sure there is a very great variability in what physicians think about the proper sequence of procedures Generally speaking myself I favor the use of adequate vagal stimulation with a drug that we know is very dramatic before we go further By that I mean with mecholyl Some people place digitalis in front of that drug in the sequence of procedures and that is a matter again of

Problems in the Bedside Management of Digitalis

DR WILLIAM A SODEMAN *

MY PART IN THE DISCUSSION has to do with some orientation in bedside problems in the use of digitalis

I want to bring out some items in the bedside use of digitalis that I think are of moment not because textbooks necessarily say they are but because they represent everyday problems we see in the referral practice of medicine Anyone receiving patients by referral whether it is an individual consultant or a medical center is frequently confronted with patients being sent in in varying degrees of management and with varying degrees of therapy being carried out previously Sometimes we know what is going on and sometimes we do not Usually we can call if it is something quite serious and find out by telephone if necessary Sometimes we get notes that are very complete telling dates and so on when the various drugs and procedures were carried out sometimes we just get a note Please Admit and Oblige so that we have varying problems in knowing what our patients have had Some of those problems represent some of the things I want to discuss So what I have to say is going to be spotty going to be picked out on that basis and I am going *to make no plea for completeness*

The problems in the bedside management have to do with the when and the how of giving this drug that is with the indications for the drug and the techniques whereby we might carry out this procedure if and when we decide the drug is indicated The indications are fairly well established It is how this is carried out the kind of preparations and so on that represent some of our major problems and it is some of those basic problems that I wish to discuss

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of the total approach but it still is a matter of some concern The same is true in what we have described again as mechanical effects One has to recognize in constrictive pericarditis what he is dealing with because the approach to that disturbance is not in the usual treatment of congestive heart failure but is in the direct approach to the heart itself There really is not any failure of the muscle itself and one is concerned whether the drug should be given at all In the other types I have spoken about the drug at least is indicated as far as its administration is concerned but it may not have the effect that one might expect in certain types of heart failure All are matters that are of importance in the evaluation of your program at the bedside

And remember when we are talking about a patient and we are giving digitalis at the bedside we are not talking about a program for digitalis alone we are talking about a program for a patient and a program for the patient s disturbance Consequently digitalis is only one of a number of things one has to evaluate in the light of the total problem

The problem of isolated left ventricular failure is one of considerable moment because I do think that there is some neglect in the use of the drug in this kind of patient In patients that do have acute pulmonary edema of course you think of the drug immediately even though some other procedures might be more important than the administration of digitalis At least digitalis is importantly in your mind in that kind of a clinical picture However it is in the earlier manifestations of isolated left ventricular failure that I think most of our neglect rests In disturbances that are early with beginning development of proto diastolic gallop rhythm when the pulmonary second sound sharpens up somewhat when it has not been sharpened up previously in short the early manifestations of heart failure on the left side I think the use of the drug is quite important and it is likely to be neglected because the patient has no edema and may have no remarkable dyspnea As I told you previously I am picking out in this total problem some of the things I think important to emphasize and I think this is one of those

The choice of the preparation is part of the total battle of the digitalis problem that represents the major part of the discussion

clinical concern dependent upon background dependent upon what one has seen what one has done, where he has been and a number of things that have nothing really to do with the problem at hand but have to do with your past experience which varies so much from physician to physician

In atrial fibrillation in a chronic stage where an individual has a slow rate and no congestive failure I do not use digitalis I think if the rate is uncontrolled or of course if there is evidence of failure on one side of the heart or the other or both the drug is indicated

The problem of breaking flutter with digitalis and then reconversion to normal sinus rhythm is one that one hears a great deal of discussion about and again fits into a pattern of what is described in the texts but does not always work out I do think that it works out sufficiently frequently to be worth while as far as attempts are concerned

To discuss the problem of congestive heart failure which is the one that is our major concern it hardly seems necessary to say that this drug is indicated in congestive heart failure for that is the central point in all of our discussion There are some problems about congestive heart failure such as what we do in terms of use of the drug and what our procedure will be The items that I have listed here as problems of etiology and mechanism I do not think are problems that determine whether you use the drug or whether you do not but I do think that they influence your evaluation of the drug in your total program for the patient Certainly there are times and instances when one thinks that rest and some digitalis is all that a patient might need There are other times of course when your concern rests in a number of other fields than digitalis Although one gives it it is not the major concern in the total program This is true when we get to matters of electrolyte disturbances the use of mercurials and a number of other procedures It is also true for example in hyperthyroidism and in types of heart failure which we do not see frequently in this part of the world I refer to those which relate to nutritional disturbances that revolve about parts of the vitamin B complex Under these circumstances of course digitalis alone in the treatment of heart failure is rather unimportant in terms

mand that you be in a position to get out of trouble insofar as the drug is concerned in a short period of time Consequently you need a preparation that is short acting a preparation comparable to digoxin for example or in some degree gitalin as well There is a need therefore in the varying approaches to congestive heart failure for the use of a number of preparations

First we had a dictum that you learn one preparation well and do not worry about any other Then came a change to the statement that you need to know something about at least two preparations I do believe as I think you can see from what I have said that you need more than that as far as the total spectrum of congestive heart failure is concerned

I see many patients that come in on all kinds of preparations We do not always agree with what the patient has had When it is possible we like to send the patient back to his physician on the kind of preparation that the physician is accustomed to using Therefore we have a tendency to use a greater number of preparations than we would if we were in an isolated practice of our own where we are not interrelated with other physicians to a great extent But I do think you need some experience and some knowledge in at least three categories of preparations

The fourth item that I wish to discuss is optimal digitalization That again comes back to something one reads all the time and is in all the current literature on digitalis namely that one tailors his therapy to the individual patient Even though that statement occurs as a chronically recurring quotation in all of our literature it has not been done to any great degree with most of the patients I see Consequently I wish to say something about this even though it is repetitious

Patients are commonly placed on digitalis without any attempt to determine whether the drug is being pushed to a point where results are obtained or a point to which the limits of the use are reached I believe it is very important from patient to patient individually even though one might use some kind of rule of thumb to begin with to start his digitalization to observe the patient daily in terms of what is going on and to manipulate the drug to the point where one is getting results or getting the minor effects of intoxication yet still is below the level at which it interferes with the efficiency of the heart We see patients quite fre

on this drug wherever clinicians get together I have my peculiar ideas about choice of preparations that do not fit into any school of thought Digitalis people are pretty much like psychiatrists you know there is a little sect here and a little sect there and so on and they have little understanding of each other I like to play the field in terms of what the patient has as far as some of these things are concerned and that has to do with preparation and preparation types

There are times in office practice when almost any type of preparation that is available would be suitable In early congestive failure a product that has prolonged action is perfectly satisfactory and often desirable Those products not having an action that is immediate and those having prolonged action are in common use Digitalis leaf is the standard preparation in this respect and as far as I am concerned it is adequate as any other preparation that we use today for that kind of patient I do not think one can talk about these preparations without talking about the kind of patient concerned Digitoxin for example is perfectly adequate and satisfactory in this kind of patient if one desires to use it Again whether one uses one or another of the products is I feel a matter of no great concern to this kind of a patient

When the patient gets further along and when other things start to happen to the patient or when the patient comes in with an acute episode where immediate action is necessary then other preparations are important Parenteral preparations then may become very necessary and the choice for immediate action becomes extremely important

When a patient with congestive failure gets along to a point where the facets in the therapeutic program are multiple and when one is concerned about electrolyte manipulation and variations in the patient from day to day the use of the preparation where one can get action and still get out of trouble in a hurry is of considerable importance for one is not concerned only with the drug but also with the variability in the patient The kind of patient I described at the beginning without the complexities of electrolyte manipulation and so on does not change remarkably from day to day But patients changing remarkably from day to day because of disease or because of things that are happening from the procedures and manipulations that you carry out de

daily practice and in bedside management of patients with the utilization of this drug These have to do with the nature of the disease with the status of the patient with the choice of the preparation with the amount of drug that might be used the way the patient may be manipulated and finally what might happen in terms of the other factors that may have a bearing upon the use of the drug

quently too who had too much digitalis, and also get to a point where it is less effective than it would be if they had the optimal amount If they have tachycardia and congestive failure continues there is a tendency to push the drug further and there is the tendency therefore to make them worse So the problem of optimal digitalization as far as I see it in my day to day activities rests not only in inadequate dosage of the drug but frequently but not as frequently as the former in the excessive use of the drug as well

We have problems these days in surgery that make us concerned about the use of the drug in surgical patients For example patients often have been stabilized to a degree where everything seems optimal and then the patient is submitted to surgery for his heart or for something else Disturbances in fluid and water balance occur as the result of these surgical procedures and the patient may on the same regimen get into difficulty and get into intoxication

For that reason it is *extremely important* I believe to be more aware of the individual problems of the patient and the kind of surgical procedures that are going to be carried out These things are becoming more important to us because of the types of surgery that are carried out today and because of the kind of support that surgeons give their patients today I see a great number of disturbances in this respect that relate to manipulation of electrolytes and fluids Most surgeons believe because they have a flame photometer and they can tell the amount of sodium and the amount of potassium that rests in the blood that they can toss *their fluids and electrolytes around with a great deal more ease* than they have in the past and they do The determinations of levels in the blood alone are not always the matters of importance in the manipulation of the fluids For these reasons there are problems which arise in these patients that are of recent origin because of developments in that particular area

I have discussed a number of phases of the use of digitalis and you see that I have not gotten down to a point of naming specific drugs specific doses and specific problems I have tried to bring out not the general indications for these drugs for they are known generally but *the problems and difficulties in areas in*

level had been lowered from 7.4 to 5.0 milliequivalents per liter, ventricular premature beats appeared. The patient complained of nausea, vomited and looked critically ill. Within short order the ectopic beats assumed a bigeminal pattern, followed by a bidirectional ventricular tachycardia, ventricular flutter and terminated in fibrillation.

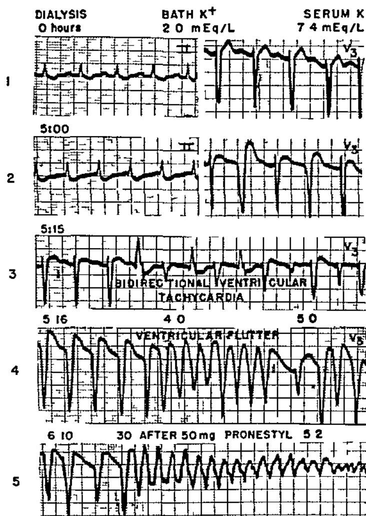


Figure 1. Increasing digitalis intoxication resulting in death during potassium extraction by means of hemodialysis.

Potassium and Digitalis

Bernard Lown M D

For the clinician the relationship between digitalis and potassium has primary pertinence to the subject of digitalis poisoning Dr Bitterman earlier today emphasized how much digitalis can be taken without intoxication The burden of my talk will be to show how little can provoke serious harm The frequency and gravity of digitalis intoxication is not widely appreciated Seldom a day elapses that we do not encounter either minor or major evidence of digitalis overdosage Such experience has led a member of the house staff of the Peter Bent Brigham Hospital to remark that nowadays lanatoside is replacing homicide as a leading cause of death It has been generally recognized that the incidence of digitalis intoxication is on the increase The reasons for the increase derive in large measure from the fact that the treatment of congestive heart failure today is based in large measure upon electrolyte manipulations The therapeutic armamentarium includes salt restriction mercurial diuretics ammonium chloride resins diamox and adrenal steroids All these measures induce changes in electrolyte metabolism and may alter the threshold of the myocardium to digitalis intoxication The extreme gravity of such changes when unrecognized are emphasized in the following experience

The patient a fifty four year old woman was admitted to the Peter Bent Brigham Hospital with post sulfonamide anuria and congestive heart failure the result of fluid overloading Cardiac compensation was restored after digitalization Digitalis maintenance was effected with 0 5 mg Digoxin daily To control the azotemia and hyperkaliemia she was subjected to hemodialysis on a Kolff type artificial kidney In order to extract maximal amount of potassium the level of this cation in the dialyzing bath was reduced to 2 0 milliequivalents per liter The sequence of electrocardiographic events during hemodialysis is illustrated in Figure 1 After five hours of dialysis when the serum potassium

prevent the usual sequence of digitalis intoxication leading to death

In patients with digitalis intoxication as in animals the administration of one of the salts or potassium will abolish evidence of drug overdosage It is curious that at times even the subjective manifestations may be lessened or abolished outright One such example of potassium action is illustrated in Figure 2 Multiform ventricular premature beats runs of bigeminy nausea and vomiting as well as increasing decompensation was precipitated by a substantial mercurial diuresis in a patient receiving 0 1 gm digitalis leaf daily Within thirty minutes after the administration of potassium ventricular ectopic beats were unifocal and of lesser frequency within two hours ectopic beats were absent and the gastrointestinal symptoms abated

It has been recognized that potassium exerts a nonspecific effect in reducing myocardial excitability Irrespective of how provoked ventricular ectopic beats can be subdued by administration of potassium As demonstrated in Figure 3 an episode of bidirectional ventricular tachycardia and multiform ventricular ectopic activity was eliminated by ingestion of supplementary potassium The patient a seventy three year old woman with coronary artery disease was on maintenance Digoxin therapy The arrhythmia first ascribed to digitalis remained unaltered after discontinuing Digoxin for one month The potassium was administered at a time when the patient was undigitalized and symptoms and signs of decompensation were appearing

The view has been held that the action of potassium in elimi

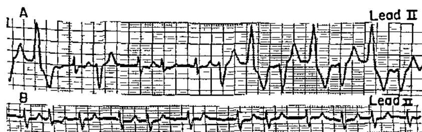


Figure 3 Bidirectional ventricular tachycardia not due to digitalis abolished within two hours after ingestion of 10 gm of potassium chloride

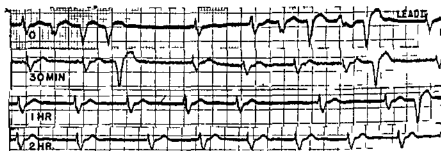


Figure 2 Oral potassium administration effective in abolishing multiform ventricular ectopic beats due to digitalis

The chain of events strongly suggests that digitalis intoxication was responsible for the arrhythmia and death. What then was the cause of the enhanced action of digitalis? Was the removal of potassium the critical factor?

The Action of Potassium on Digitalis Induced Arrhythmias

It has been established that potassium will abolish ventricular ectopic beats due to digitalis. When the serum potassium in dogs is raised and maintained at about 7 mEq./L. the dose of digitalis required to produce ventricular extrasystoles or ventricular tachycardia is increased by 240% compared to requirements during control studies when the potassium level is maintained normal. In the presence of hyperkaliemia despite the high doses of digitalis necessary for toxicity the ectopic mechanisms are of transient duration. In addition the pattern of toxicity is altered. Instead of ventricular tachycardia there occur atrial standstill, irregular idioventricular rhythm and intraventricular conduction defect. If more digitalis is administered ventricular excitability is reduced eventuating in ventricular standstill. Our present experiments indicate that animals given large doses of digitalis in the presence of hyperkaliemia die from potassium rather than from digitalis intoxication. This may have a bearing on the observations which Dr. Chen reported yesterday. When aglycone is injected without the sugar convulsive seizures ensue. Thereafter upon continued administration of aglycone the animals develop ventricular standstill rather than fibrillation. Convulsions cause liberation of muscular potassium. The hyperkaliemia may

sensitivity of the myocardium to digitalis? Examination of some of the clinical features of this phenomenon suggests an explanation other than digitalis mobilization The patient who exhibits post mercurial digitalization is usually in the grip of advanced heart failure He has been maintained on rigid salt restriction and received frequent mercurial injections with ammonium chloride pretreatment to augment diuretic response These circumstances predispose to significant potassium losses following mercurials It may therefore be that depletion of potassium is the critical factor in the post mercurial redigitalization syndrome

Evidence for this supposition was provided in the following study

Non digitalized patients in congestive heart failure were given acetylstrophanthidin an ultra rapid acting strophanthin derivative which is eliminated within two or three hours This permitted determination of the myocardial sensitivity to digitalis Such studies were repeated after mercurial induced diuresis Electrolyte balances were carried out The diuretic therapy altered the response to digitalis in some patients but not in others Patients who exhibited enhanced sensitivity to digitalis showed significant urinary losses of potassium while those without changes in digitalis threshold did not sustain such deficits

Figures 4 and 5 illustrate the change in myocardial sensitivity

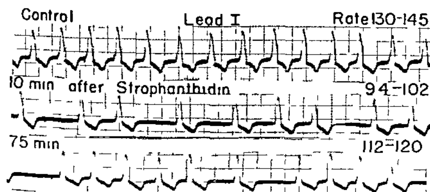


Figure 4 Acetyl strophanthidin promptly slowed ventricular rate during atrial fibrillation This effect dissipated in seventy five minutes There was no intervening toxicity

nating some of the evidence of digitalis intoxication is in the nature of a nonspecific pharmacologic effect In support of this thesis are the following facts first potassium controls ventricular ectopic mechanisms whether induced by digitalis or not second the amount of potassium required for therapeutic effect may be the same in the digitalis and non digitalis group of disorders and third even in cases of digitalis intoxication the action of potassium may be transient and continue only for the duration of the hyperkaliemia Recent studies however indicate that in the *case of digitalis intoxication the action of potassium is not phar*macologic but rather in the nature of a physiologic restitution of myocardial incurred potassium deficits

Mercurial Redigitalization

Evidence for a clinical interrelationship between digitalis and potassium was first adduced in studies of mercurial redigitalization As you know some patients with advanced heart failure who are fully digitalized when given mercurial diuretics may develop evidence of digitalis overdosage Within twelve to twenty four hours after diuresis they may experience nausea vomiting diahrrea or any of the other subjective stigmata or any of the gamut of electrocardiographic manifestation of digitalis intoxication Levine and Schnitker[1] attributed this phenomenon to the mobilization of digitalis laden edema fluid They found as much as 0 1 gm of digitalis leaf per liter of edema fluid Their methods were cumbersome involving complex biochemical *extractions and crude biological assays* If *digitalis* is present in edema fluid in the amount indicated it should be possible to induce intoxication by giving the maximum amount of digitalis presumed to be present in the duretic urine For example if a patient experiences a diuresis of two liters and develops redigitalization then at some other time when mercurials are not given the administration of 0 2 gm of digitalis leaf or its equivalent in addition to the maintenance dose should reproduce the same symptoms and signs This is not the case Even larger supplements of digitalis may be without effect while even lesser degrees of diuresis may provoke redigitalization

In what way then does the mercurial induced diuresis enhance

(2) Little clinical experience is available with the cardiotonic effects of acetylstrophanthidin. It is possible that spontaneous wide variability to this drug on different occasions is a critical factor.

To overcome these objections ouabain was employed and the procedure was reversed. The patient was digitalized first after diuresis and then redigitalized after being maintained in positive potassium balance. The following experience is illustrative. On two separate occasions, one month apart, a twenty year old woman with mitral stenosis and heart failure received ouabain. Both times after receiving 0.7 mg. of ouabain intravenously in fractional doses experienced nausea, vomited, developed 1st degree heart block, a changing atrial pacemaker and occasional

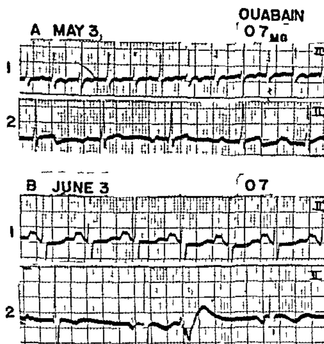


Figure 6. On two occasions after mercurial diuresis 0.7 mg. of Ouabain induced minor evidence of digitalis overdosage. In both instances there occured first degree heart block, a changing atrial pacemaker with nausea and vomiting.

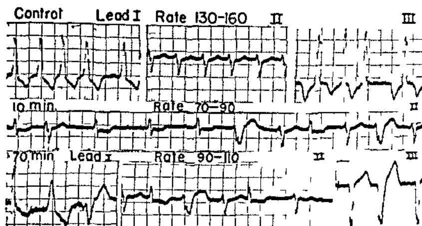


Figure 5 A dose of acetylstrophanthidin insufficient to produce intoxication on previous occasions provoked ventricular ectopic beats and subjective manifestations of overdosage after the loss of body potassium

to digitalis following diuretic therapy The patient a sixty nine year old man with coronary artery and hypertensive cardiovascular disease in failure received on two occasions 1 2 mg of acetylstrophanthidin intravenously Each time the ventricular rate slowed maximally within fifteen minutes and the response waned within ninety minutes No subjective or objective evidence of digitalis intoxication occurred (Figure 4) The third digitalization carried out several days later followed a 2000 cc diuresis produced by mercurhydrin and ammonium chloride (Figure 5) Within ten minutes after acetylstrophanthidin injection numerous and multiform ventricular ectopic beats appeared with a run of trigeminal rhythm Vomiting occurred one hour after acetylstrophanthidin administration and toxicity persisted for ninety minutes Of interest is that cardiac slowing was still in evidence four hours after digitalis administration Electrolyte studies indicated that the diuretic agents produced a potassium deficit of 83 milliequivalents

One may question the validity of the conclusions based on these studies on two grounds (1) The changed reactivity of the heart to digitalis may not have been due to the loss of potassium but to the digitalizations prior to the mercurial administration

ing the ten days of potassium supplementation she retained 210 milliequivalents. The serum potassium values bore no correlation to the balance findings. Attention needs be called to the fact that at the time when she required the most digitalis her weight had decreased 9 kilograms or a 20% reduction. This is in accord with clinical experience indicating that the patients weight does not permit prediction of digitalis requirements. More critical than the weight is the electrolyte balance.

ANIMAL TITRATION STUDIES *

The relationship between digitalis and potassium was further amplified in experimental studies in dogs. Employing both the artificial kidney and acetyl strophanthidin biologic titration of the digitalis threshold was carried out against a variable body potassium content. By means of the artificial kidney it was possible to remove selectively potassium from the body while maintaining the essential constancy of other ions. Utilization of acetyl strophanthidin permitted numerous discrete digitalizations to identical end points in the course of a single day.

The study consisted of four phases. During the first five digitalizations were accomplished at two hourly intervals with

FIGURE 8

Date	Procedure	Potassium		Weight Kg	Ouabain	
		Balance mEq	Serum mEq/L		Amount for Toxicity	Duration of Toxicity
May 3	Thiomerin 2cc (SC)	−100	5.1	44	0.7	4
June 3	Thiomerin	− 70	3.6	39	0.7	3
June 13	Potassium Chloride 7.5 gm/day × 10 days	+210	5.[illegible]	35	1.3	1

Figure 8. Table summarizing three digitalizations with ouabain. The first two were carried out after potassium loss and the third after a gain of potassium.

* These studies using the artificial kidney were carried out in co-operation with Dr John P Merrill of the Peter Bent Brigham Hospital.

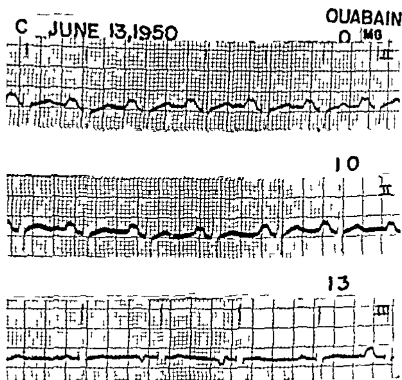


Figure 7 After positive potassium balance patient able to take nearly twice the amount of ouabain which on previous occasions provoked intoxication

ventricular premature beats The end points and dosage requirements were essentially the same notwithstanding the fact that the atrial mechanism was different prior to each digitalization (Figure 6) The first time she had a supraventricular tachycardia and the second time normal sinus rhythm Both digitalizations were accomplished after sizeable diuresis When ouabain was given for a third time but now following ten days of potassium supplementation an entirely different response was observed The same objective end point of toxicity required nearly twice as much drug (Figure 7) Furthermore toxicity was of much shorter duration lasting for only one hour while previously it persisted for three and four hours (Figure 8)

Prior to the first two digitalizations this patient sustained a negative potassium balance of 100 and 70 milliequivalents Dur

during two successive digitalizations in the same animal (Figure 10) When the serum potassium was unaltered 0 48 mg of acetyl strophanthidin *induced ventricular tachycardia from a single* focus having a duration of eleven minutes (Figure 10 strip 1) When 25 milliequivalents of potassium was extracted by means of

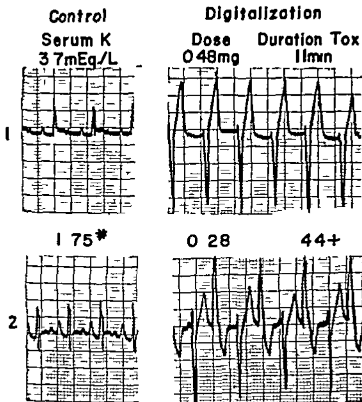


Figure 10 Two digitalizations with acetylstrophanthidin to an endpoint of ventricular tachycardia Digitalization (1) carried out while the serum potassium maintained normal Digitalization (2) accomplished after the removal of potassium with the artificial kidney The episode of bidirectional ventricular tachycardia was controlled by raising the serum potassium concentration

FIGURE 9

178 DIGITALIZATIONS IN DOGS WITH ACETYL STROPHANTHIDIN WHILE BODY K^+ IS ALTERED

Serum K (mEq/L)	*Number of Digitalization*	*Dose of Acetyl S (mgm)*	*Duration of Toxicity (Min)*
4.1	137	0.61	*
2.1	19	0.19	21+
7.0	22	1.12	3

*A[illegible] 3.7 [illegible]

Figure 9 Summary of 178 digitalizations in dogs while body potassium was maintained normal was increased and was depleted

out hemodialysis During the second phase digitalizations were carried out while hemodialysis was in process but all electrolytes were maintained constant The third phase or titration dialysis consisted of digitalizations with acetyl strophanthidin while body potassium was either reduced or increased Lastly selective potassium changes were carried out without digitalization Each animal served as its own control A total of 178 digitalizations were achieved to a common end point of ventricular tachycardia

Overall results are depicted in Figure 9 In 137 digitalizations with acetyl strophanthidin while the potassium was normal 0.61 mg of drug was required to produce ventricular tachycardia lasting seven minutes After the removal of potassium with the artificial kidney with a lowering of serum concentration to 2.1 milliequivalents per liter 0.19 mg of acetyl strophanthidin was necessary to induce intoxication Though only 32% of the control dose was administered ventricular arrhythmias lasted in excess of twenty one minutes When digitalization was accomplished with a serum potassium maintained at 7.0 milliequivalents per liter, 1.12 mg was required for the production of ventricular ectopic beats which were in evidence for an average duration of only three minutes

Three differences were noted in the response of the potassium depleted animal to acetyl strophanthidin when compared to control digitalizations in the same animal These are illustrated

during two successive digitalizations in the same animal (Figure 10) When the serum potassium was unaltered 0 48 mg of acetyl strophanthidin induced ventricular tachycardia from a single focus having a duration of eleven minutes (Figure 10 strip 1) When 25 milliequivalents of potassium was extracted by means of

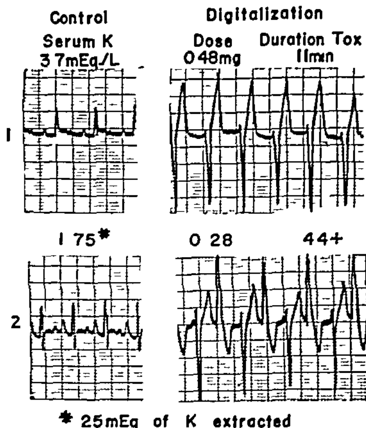


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hemodialysis 0 28 mg of acetyl strophanthidin resulted in a *bidirectional ventricular tachycardia* lasting over forty four minutes The arrhythmia was controlled by restoring body potassium Thus the removal of potassium resulted in a reduction of the required dose for intoxication prolonged the duration of the arrhythmia and promoted the emergence of varyform bigeminal and bidirectional ventricular ectopic mechanisms Such arrhythmias were unusual in animals having no electrolyte derangements The depleted animal responds to digitalis intoxication in a manner similar to the patient with advanced decompensation

The potassium depleted animal is extremely susceptible to digitalis intoxication Minor stresses or loads upon the cardiovascular apparatus suffice to produce serious disorders of rhythm When small amounts of blood are rapidly infused into a critically digitalized animal toxicity is produced The type and duration of the toxic pattern depends upon the amount of blood given the degree of digitalization and most especially upon the state of the potassium balance In hyperkalhemic animals even extreme degrees of such circulatory loading carried out immediately after recovery from digitalis intoxication does not significantly alter cardiac rhythm or A V *conduction When similar* loads are imposed upon animals with normal potassium levels the occurrence of arrhythmias depends upon the time interval elapsed since recovery from the episode of digitalis intoxication If a load of sufficient magnitude is imposed soon after recovery from intoxication the normal animal will exhibit a very transient recurrence of arrhythmia When a longer time interval has elapsed minor *degrees of intoxication are produced In dogs depleted of* potassium major and prolonged derangements of rhythm are the rule even after small loads imposed long after recovery from digitalis intoxication

Characteristic results of one loading study carried out during hemodialysis is demonstrated in Figure 11 Loads were imposed by clamping the arterial outflow to the artificial kidney while maintaining *venous inflow at the rate of 175 cc* of blood per minute All loads were imposed shortly after recovery from a paroxysm of ventricular tachycardia produced by acetyl stro

phanthidin When potassium was maintained normal the imposition of a load for a period of one and a half minutes three minutes after recovery from ventricular tachycardia resulted in transient first and second degree heart block Similar degrees of loading when the animal was hyperkalhemic caused slowing of the heart rate and lengthening of the P R interval Finally when the same procedure was carried out when the animal was depleted

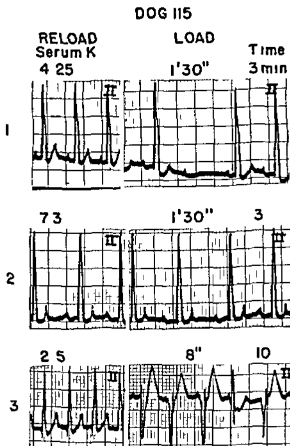


Figure 11 Three loading studies carried out after recovery from ventricular arrhythmias induced by acetylstrophanthidin (1) When body potassium maintained normal (2) When serum potassium elevated (3) After potassium removal

FIGURE 12

EFFECT OF K^+ EXTRACTION ON DIGITALIS THRESHOLD DURING 33 HEMODIALYSIS IN 25 UREMIC PATIENTS

Digitalized	*Number Hemodialysis*	*Potassium*		*Digitalis*	
		Initial	*Final*	*Toxicity*	*Effect*
Yes	16	6 9	4 6	7	6
No	17	7 0	4 7	0	0

O e[illegible] t [illegible] t p [illegible] r [illegible] a oxysmal A F [illegible] p [illegible] n d [illegible] ame dur g d aly s

of potassium a loading for a duration of merely eight seconds sufficed to evoke ventricular tachycardia This third loading study was initiated ten minutes after recovery from digitalis intoxication In the non depleted animal after such an interval of time no degree of loading produced sustained ventricular arrhythmias

These observations may have clinical pertinence Occasionally one sees patients in whom arrhythmias ascribable to digitalis intoxication develop for the first time after exercise straining on the bed pan emotional agitation removal of oxygen therapy etc Is this reaction a counterpart of the so called loading phenomenon?

HUMAN HEMODIALYSIS STUDIES

If the relationship between digitalis and potassium described in dogs holds for human beings it should be demonstrable in digitalized uremic patients who are subjected to hemodialysis for the correction of azotemia and hyperkaliemia Several years ago we had the opportunity of carrying out such a study in Dr Merrill s laboratory at the Peter Bent Brigham Hospital The study was based on thirty three hemodialysis procedures in twenty five uremic patients Half of this group of patients were digitalized Potassium was removed for a two hour period by lowering its concentration in the dialyzing bath to 2 0 milliequivalents per liter The results for the two groups are summarized in Figure 12 During sixteen hemodialysis procedures in patients on maintenance digitalis seven developed intoxication This consisted of

atrial or ventricular arrhythmias or A V conduction disturbances Six other patients in this group exhibited shortening of the Q T interval ST segment scooping and inversion of the early portion of the T wave In the non digitalized control group only one patient developed an arrhythmia during dialysis The disorder was auricular fibrillation which the patient experienced on a number of occasions prior to the hemodialysis None developed digitalis effect in their electrocardiograms The two groups were comparable in all clinical respects including the degree of potassium removal during hemodialysis

Losses and Shifts in Body Potassium Losses of potassium from the body irrespective of how these have been produced potentiate the toxic action of digitalis Intoxication has been noted in digitalized patients after administration of desoxycortico sterone acetate cortisone cation exchange resins diamox and ammonium chloride When patients have sustained losses of potassium due to gastrointestinal or renal disease sensitivity to digitalis may be markedly enhanced In such patients especially when the serum potassium level is depressed even small increments of digitalis may induce serious intoxication or death The danger of digitalis under such circumstances is illustrated in the following case history

> The patient a sixty year old man with coronary artery disease *and hypertensive* cardiovascular *disease* was *admitted to the* hospital in severe right and left sided congestive heart failure He had been vomiting for three months and for this period digitalis had been discontinued He was azotemic and oliguric Serum potassium was normal though the history suggested severe depletion Because of the presence of pulmonary edema—digitalization was attempted Acetyl strophanthidin was employed After giving 0 6 mg intravenously he developed numerous multiformed ventricular premature beats followed by ventricular flutter (Figure 13) Rapid dissipation of drug action permitted recovery from the digitalis intoxication Administration of a smaller dose of digitalis several days later again evoked serious arrhythmia

The myocardial threshold to digitalis may also be reduced by shifts of potassium from the extracellular to the intracellular compartments occurring without any losses of electrolyte from the body When the potassium is acutely withdrawn from the plasma

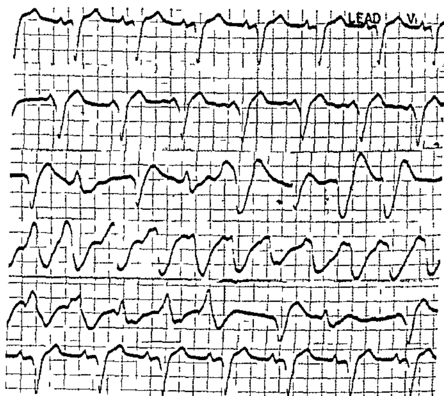


Figure 13 Marked sensitivity to digitalis in potassium depleted patient in advanced decompensation Small amount of acetylstrophanthidin results in transient bout of ventricular flutter (all strips are part of one continuous tracing taken at lead V over a 30 minute period)

during deposition of glycogen sensitization to digitalis takes place In the critically digitalized patient administration of insulin or carbohydrate may precipitate ventricular premature beats or ventricular tachycardia

In view of these observations it is no longer adequate to regard digitalization from the vantage point of dosage alone The patient s sensitivity to drug is a critical factor A biological titration of each patient s unpredictable requirements is thus essential for proper therapy

Serum Versus Cellular Potassium Levels The question is frequently posed whether the myocardial threshold to digitalis is determined by the serum or cellular concentrations of potas

sium There is evidence that cellular rather than extracellular potassium concentration is the determining factor (1) Patients with digitalis intoxication have normal serum potassium values This is true irrespective whether intoxication is precipitated by an overdose of drug or mercurial induced potassium loss (2) When digitalis intoxication is treated with potassium the abolition of evidence of overdosage bears no relation to the serum potassium level (3) In digitalized patients in whom abnormal mechanisms have been produced through the removal of potassium by means of hemodialysis prompt restoration of the serum level to its initial value does not abolish the arrhythmias This is demonstrated in Figure 14 Second degree heart block was produced in a digitalized patient by extraction of potassium rapid restoration of the predialysis potassium concentration by means of dialysis against a bath potassium of 6 0 milliequivalents per liter simultaneous with intravenous infusion of 20 milliequivalents lessened but did not abolish the degree of heart block (4) In experimental animals it is possible to lower the serum potassium level to 2 milliequivalents per liter and maintain this value constant while body potassium is being removed Such continued

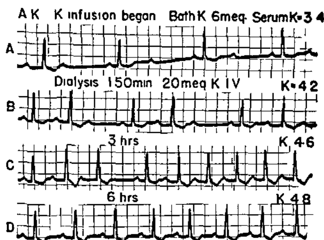


Figure 14 Second degree heart block induced by potassium extraction Restoration of serum potassium level did not promptly abolish the heart block

depletion of potassium is associated with a striking augmentation of myocardial sensitivity to digitalis

The serum potassium concentration bears but an indirect relation to the myocardial threshold for digitalis intoxication The serum level *is an index of myocardial sensitivity only in so* far as it reflects deviation in the cellular cation concentration In the majority of instances therefore the serum potassium value affords no guide in digitalis therapy

Potassium Metabolism In Heart Failure Not only current treatment regimen but the very process of heart failure affects the balance of body potassium and alters myocardial sensitivity to digitalis It is well documented that electrolyte and water abnormalities occur during decompensation Metabolic studies provide indirect evidence that cellular potassium deficits develop in congestive heart failure and restitution of this cation follows recovery Muscle biopsy studies confirm the existence of such deficits Heart muscle participates in these losses of potassium As the heart increases in weight myocardial concentration of potassium phosphous and creatine is reduced The decrease in *potassium is most marked in the chambers that are failing* These deficits affect both auricles and ventricles

The unstable equilibrium in the potassium concentration gradient between cellular and extracellular compartments is maintained at the expense of the oxidative energy of the cell The interference with cellular oxidative function resulting from congestive failure may alter the level of equilibrium In heart failure numerous processes are operating which have been shown experimentally to induce leakage of cellular potassium Included are such factors as anoxia dehydration muscular ischemia acidosis edema and overwork Furthermore the patient in failure is in a precarious nutritional balance Loss of appetite anorexogenic drugs impalatable diets diminished gastrointestinal absorption and deranged liver function all tend to impair the nutritional state and favor the loss of nitrogen and potassium

It has already been indicated that therapy itself may predispose to and promote losses of body potassium The tendency to lose potassium after mercurial diuretic administration is accentuated by prolonged and rigid salt restriction In patients

with a good capacity for sodium excretion as in the early stages of decompensation even extensive diuresis does not cause significant deficits of potassium Potassium is believed to participate in the distal tubular ionic exchange process The renal tubular cells secrete potassium in exchange for sodium in the tubular urine When sodium is in short supply this mechanism may be activated for the conservation of base After long continued diuretic therapy such preferential potassium losses may lead to cumulative and clinically significant deficits occasionally resulting in hypochloremic and hypokalemic alkalosis Potassium losses are further enhanced by the administration of ammonium chloride especially when used continuously

In view of these considerations it is not surprising that patients with advanced heart failure are susceptible to digitalis intoxication This type of patient requires larger amounts of digitalis for therapeutic effect and lesser dosage for the development of toxicity The therapeutic toxic ratio is at times unity Even small losses of potassium may therefore suffice to tip the scale into the toxic side It may very well be that the increasing dependence in the treatment of congestive heart failure on the restriction of sodium and the promotion of its loss is in large measure responsible for the observed rise in the incidence of digitalis intoxication

Effect of Digitalis on the Potassium Concentration Within the Myocardium So far no mention has been made of the fact that digitalis itself may cause liberation of potassium both from skeletal as well as heart muscle There is general agreement that toxic doses of digitalis deplete myocardial potassium This has been recently confirmed by Hellems and co workers[2] In dogs acutely digitalized with acetyl strophanthidin while coronary sinus arterial concentration differences were followed there occurred an abrupt outpouring of myocardial potassium The loss of potassium was noted within one minute after drug administration was maximal within six minutes and ceased after twenty five minutes Converse but larger exchanges of sodium occurred simultaneously Cohn[3] utilizing radio potassium techniques in conjunction with coronary sinus catheterization of the dog heart has demonstrated that daily administration of 0 2 to 0 4 mg of digitoxin caused inhibition of potassium influx into the myocardial

cell A new steady state developed in potassium transport between interstitial and intracellular compartments with potassium concentration in the later compartment reduced by 15%

The basis for digitalis action on cellular electrolyte transport is at the moment unclear In the isolated guinea pig heart competition between cardiac glycoside and acetylcholine have been noted [4] The rate of metabolism of acetylcholine influences the permeability of the myocardial cell to sodium and potassium It has been shown that large amounts of lanatoside C significantly inhibit the activity of acetylcholinesterase The degree of inhibition was conditioned in part by the concentration of potassium in the perfusing medium Glycoside interference with acetylcholinesterase activity was diminished by increasing the concentration of either potassium or acetylcholine while an opposite effect followed reduction in their respective concentrations These relationships suggest that lanatoside C competes with acetylcholine for the active sites on the cholinesterase molecule The *action of digitalis on membrane permeability may thus be the* indirect resultant of such competition

Conclusion Digitalis is one of the most widely used and at times most abused drugs in cardiac therapy When used properly it is the most valuable agent presently available for the restoration of compensation When used improperly it may cause serious intoxication and even death Recognition of the relationship between digitalis and potassium is essential for maintenance of chronically ill cardiac in the optimal state of well being

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Auricular Arrhythmias Due to Digitalis*

Bernard Lown, M.D.

Digitalis in toxic amounts has been reported to produce the entire gamut of cardiac arrhythmias. The ventricle and the A-V conduction system are believed to be primarily involved. To date, abnormal auricular mechanisms due to digitalis are regarded as rare, of nonspecific appearance and of little if any clinical consequence. Recent experience, however, indicates that such atrial disorders caused by digitalis overdosage are frequent, have serious implications and assume highly distinctive and readily identifiable electrocardiographic patterns.

The most important atrial reaction to digitalis intoxication is paroxysmal auricular tachycardia with block (hereafter referred to as PAT with block). This is an hybrid arrhythmia partaking of features of both classical auricular tachycardia and auricular flutter. A typical example is presented in Figure 1. Like classical auricular tachycardia it has a rate ranging from 150 to 200 beats per minute. Like flutter it exhibits A-V conduction defect. Distinctive of this disorder are the upright diminutive P waves in Leads II and III which are separated by an isoelectric base line. The type of conduction defect varies from an occasional Wenckebach phenomenon against a predominant background of 1:1 response to complete A-V block. The arrhythmia may last for several minutes or persist for several weeks.

Sir Thomas Lewis recorded the first episode of PAT with block on the polygraph in 1909. To date 160 cases have been reported. Cardiologists continue to regard PAT with block as an electrocardiographic oddity of extreme rarity. This is attested to by the fact that individual cases have been considered sufficiently unique to merit report. In a study carried out at the Peter Bent Brigham Hospital with Dr. Harold D. Levine covering

* From the medical clinics of the Peter Bent Brigham Hospital.

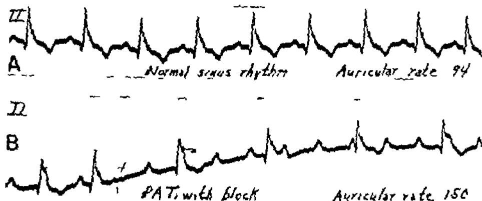


Figure 1 A typical example of PAT with block Atrial rate 150 Upright *P waves in lead II separated by an isoelectric baseline*

the period 1942 through 1954 112 episodes of this disorder were observed in 88 patients

Evidence for the Etiologic Role of Digitalis in the Production of PAT with Block

If digitalis is indeed a factor in the development of *PAT with* block it should be possible to produce this arrhythmia by digitalis when the intervention of other variables can be definitely excluded Furthermore it should be possible to demonstrate the operation of the potassium digitalis relationship Namely PAT with block should be producible in digitalized patients by depletion of body potassium Administration of potassium should promptly abolish the ectopic mechanism Finally, potassium should prove ineffective in those examples of the arrhythmia where digitalis was not the causative factor

Production by Digitalis *To date we have observed the de*velopment of PAT with block during the process of digitalization in four patients In three it occurred after the injection of acetyl *strophanthidin and in one after large doses of intravenous di*goxin Since in three patients the arrhythmia was in full form within twelve minutes after the injection of acetyl strophanthidin *it seems likely that digtalis was the specific cause* The production *of one* such episode is demonstrated in Figure 2 The patient was on maintenance digitalis therapy when acute pulmonary edema

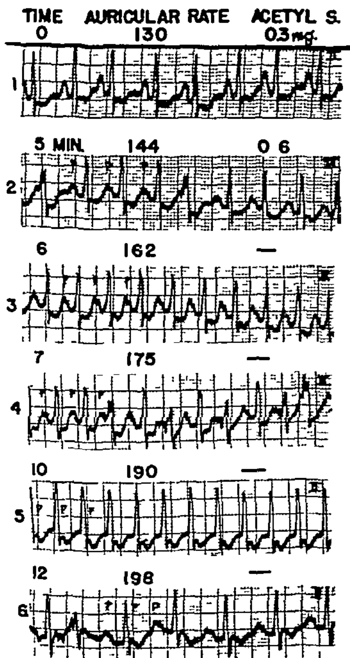


Figure 2 Production of PAT with block following small increments of acetylstrophanthidin

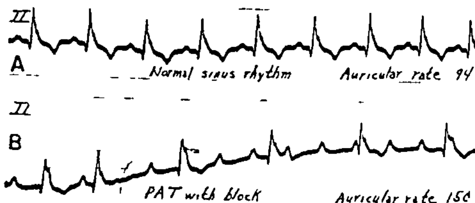


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loss of body potassium enhances digitalis action on the heart It is equivalent to the administration of additional increments of digitalis

PAT with block developed in three patients during the removal of potassium by means of hemodialysis These patients were on maintenance digitalis therapy Digitalis was omitted on the day of dialysis PAT with block emerged after one to two hours of potassium extraction The evolution of the arrhythmia was gradual and exhibited the same sequence as in the patients who received acetyl strophanthidin Again the first phase consisted of a change in atrial pacemaker (Figure 3) There followed an acceleration in atrial rate with increased A V block As the auricular rate reached a range from 160 to 190 second degree

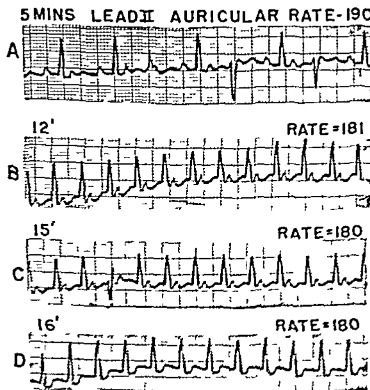


Figure 4 *[illegible] reversion of PAT with block following oral potassium administration*

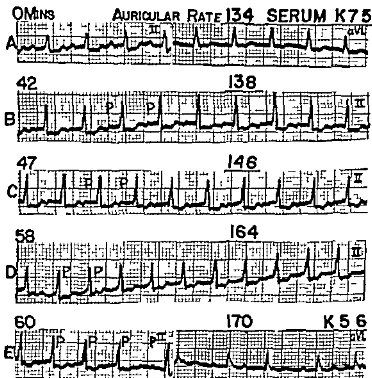


Figure 3 Development of PAT with block during potassium removal in digitalized uremic patient

developed The ventricular rate was 130 The possible value of additional digitalis was resolved by means of an acetyl strophanthidin tolerance test After the intravenous injection of 0 6 mg acetyl strophanthidin the following sequence took place The contour of the P wave changed abruptly with acceleration of rate to 144 These alterations indicated usurpation of pace setting function by the ectopic focus Next there ensued a gradual increase in both heart rate and A V conduction duration with leftward migration of the P wave which eventually merged with the terminal portion of the preceding QRS Finally when the auricular rate and the A V conduction defect reached a critical level the 1 1 atrioventricular response was replaced by second degree heart block The four patients showed essentially similar phases in the evolution of PAT with block

Production by Potassium Depletion In the digitalized patient

loss of body potassium enhances digitalis action on the heart It is equivalent to the administration of additional increments of digitalis

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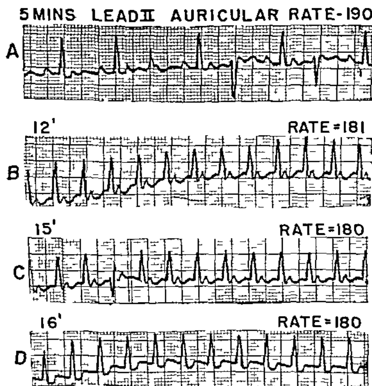


Figure 4 Beginning reversion of PAT with block following oral potassium administration

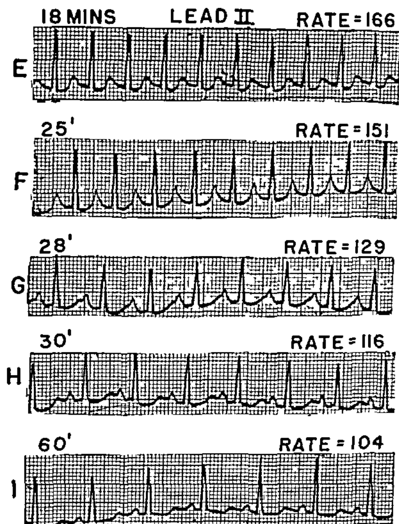


Figure 5 (cont) Process of reversion completed within sixty minutes after ingestion of potassium chloride

heart block developed When the arrhythmia was in full form the serum potassium had been lowered by about one milliequivalent per liter In none of the patients however was the serum potassium concentration less than 3.5 milliequivalents per liter In the patient whose electrocardiogram is illustrated in Figure 3 the concentration was 5.6 milliequivalents per liter at the time of onset of PAT with block

Effectiveness of Potassium When PAT with block is caused by digitalis potassium irrespective how it is administered is effective in restoring a normal mechanism The stages in the reversion of Pat with block by potassium are chronologic mirror images of the phases in the evolution of the arrhythmia As shown in Figures 4 and 5 the first change consisted in a slight slowing of the rate of the ectopic focus with establishment of 1 1 atrioventricular response and sudden acceleration in ventricular rate Thereafter atrioventricular block diminished and the heart rate decreased An abrupt change in P wave contour heralded the reestablishment of sinus rhythm

Ineffectiveness of Potassium in PAT with Block Not Due to Digitalis Atrial arrhythmias not caused by digitalis are usually unaffected by potassium This is true even if the atrial disorder is PAT with block In nine patients with auricular mechanisms not due to digitalis potassium was without effect In six the arrhythmia was PAT with block in two flutter and in one nodal tachycardia These patients received an average of 88 milliequivalents of potassium in the course of several hours Four of the nine patients developed moderate hyperkalemia nevertheless no alterations were noted on the auricular mechanism (Figure 6) By contrast twenty three of twenty five episodes of PAT with block due to digitalis were reverted to sinus rhythm with an average dose of 58 milliequivalents of potassium

It can therefore be concluded that an overdose of digitalis affects auricles as well as ventricles The auricular manifestations of digitalis intoxication may assume the specific form of PAT with

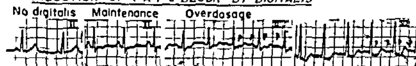
FIGURE 6

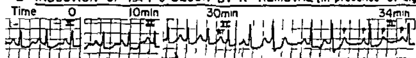
EFFECT OF POTASSIUM ON AURICULAR ARRHYTHMIAS

Cause of Arrhythmia	*Number of Episodes*	*Potassium (mEq)*	*Type of Disorder*	*Reversion*
Digitalis	25	20–120 av 58	Pat c B	23
Other	9	40–130† av 88	6 Pat c B 2 Flutter 1 Nodal Tachy	0

[illegible]

†P [illegible]





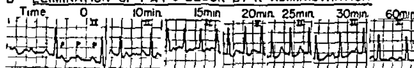


Figure 7 Summary of the relationship between digitalis and potassium in PAT with block

block *In this arrhythmia as in other cases of digitalis poisoning* the relationship between potassium and digitalis is a determining factor in the genesis of the disorder

The electrocardiographic evidence for a causative role of digitalis in the production of PAT with block is summated in Figure 7

Clinical Aspects

The evidence presented indicates that PAT with block may be caused by digitalis but does not suggest how frequently this drug is implicated as the critical factor The answer to this and to other pertinent questions is to be found in the 112 episodes of PAT with block studied at the Peter Bent Brigham Hospital

Frequency of Digitalis Induced PAT with Block In a period of thirteen years extending through 1954 eighty three episodes in 64 patients were caused by digitalis in sixteen episodes the relationship to digitalis was uncertain and in thirteen digitalis was definitely not a factor Thus 75% of episodes of PAT with block are the result of digitalis intoxication Half of all the cases were observed in the years 1952 through 1954 It need be emphasized that the increased incidence may be due in part to heightened awareness and recognition of this mechanism

Clinical Features Of the group of patients having PAT with block due to digitalis all but six were in congestive heart failure The majority had both right and left sided failure and were treated with rigid salt restriction and frequent mercurial injections There was a slight preponderance of females The average age for the group was fifty one years Seventeen of the patients were over sixty five years of age and six were in their eighties Excluding ten patients with uremia there was an equal incidence of rheumatic hypertensive and coronary heart disease Twelve of the patients experienced more than one episode of the disorder The arrhythmia occurred most frequently during maintenance digitalis therapy All the different digitalis preparations in current use were implicated The electrolyte pattern was usually normal In a third of the patients however there was hyponatremia and associated hypochloremia The serum potassium concentration with few exceptions was within a normal range

The patients with the digitalis variety of PAT with block may be classified on the basis of the immediate precipitating cause of the arrhythmia into one of four categories (Figure 8) In twenty four episodes a distinct overdose of digitalis preceded the onset of PAT with block In thirty one a mercurial induced diuresis with a weight loss ranging from 1 to 7 kilograms was the factor immediately antedating the onset of the arrhythmia Nine episodes were caused by an unexplained increased sensitivity to digitalis These patients developed PAT with block while receiving small maintenance doses In a few of these patients the increased responsiveness to digitalis was corroborated by an acetyl

FIGURE 8

FACTORS PRECIPITATING 83 EPISODES OF PAT c BLOCK IN 64 PATIENTS

Immediate Cause of Arrhythmia	Number	Percent
Digitalis Overdose	24	29 0
Mercurial Diur	31	37 5
Sensitivity to Digitalis	9	10 [illegible]
Miscellaneous	19	3 0

R [illegible] K loss [illegible] vomit[illegible]

strophanthidin tolerance test In the nineteen remaining episodes miscellaneous factors such as renal potassium loss, hemodialysis vomiting the administration of cortisone insulin or calcium were temporally related to the establishment of PAT with block In close to 60% of the patients shifts or loss of body potassium was the predisposing background for the arrhythmia It appeared that potassium loss preferentially sensitized the auricles to digitalis intoxication

It was difficult to ascribe a specific symptom complex to the arrhythmia Since PAT with block occurs in patients with congestive heart failure already suffering from a multitude of complaints often it adds but little to the already serious clinical picture Generally the clinical situation was altered through the aggravation of failure acceleration of the ventricular rate, or the development of symptoms of digitalis intoxication In a number of patients the first suggestion of the disorder was the redevelopment of decompensation This occurred at times without significant ventricular acceleration In PAT with block the ventricular response was usually rapid In 57% of episodes it exceeded a rate of 100 per minute This was due to the varying degrees of A V block with runs of 1 1 atrioventricular response The most common complaints were weakness and loss of a sense of well being Objective auscultatory signs were absent

PAT with block should be suspected when a change in rhythm occurs after an increase in digitalis dosage or following diuresis This suspicion is reinforced if the rate is accelerated and the rhythm becomes irregularized when the preceding mechanism was sinus rhythm or regularized when the preceding mechanism was atrial fibrillation

Prognosis

A grave prognosis is associated with the digitalis induced variety of PAT with block Of the group of sixty four patients thirty seven or 58% were dead shortly after the onset of the arrhythmia When PAT with block was precipitated by an over dose of drug without evident electrolyte derangements the mortality rate was less than 50% When potassium loss was the factor initiating the arrhythmia the mortality rate exceeded 75% A number of patients in this latter group were in the end stages of

decompensation exhibiting evidence of dilution hyponatremia. The emergence of PAT with block was but an additional indication of disturbed electrolyte composition in the cellular compartment portending the impending denouement. In this group a fatal outcome was the rule even if the arrhythmia was controlled by the administration of potassium.

The serious prognosis was in some measure due to the failure to recognize the role of digitalis in the development of PAT with block. This is indicated by the fact that when the arrhythmia was attributed to digitalis and appropriate measures were taken the mortality rate was 35%. When such recognition was lacking and digitalis was continued the mortality rate was twice as large or 70%. In PAT with block the serious prognosis is due not only to the arrhythmia but also to the measures undertaken for its control. PAT with block is at times mistaken for auricular mechanisms where digitalis is considered the drug of choice. The administration of additional digitalis may provoke ventricular fibrillation without intervening ventricular arrhythmia.

Electrocardiographic Features of PAT with Block

The salient electrocardiographic features are summarized in Figure 9. The mean auricular rate was 182. In 76% of the episodes it was less than 200 beats per minute. The base line between P waves was isoelectric. P waves were usually small, at times barely ruffling the base line. When the auricular complex was visible it

FIGURE 9

ELECTROCARDIOGRAPHIC FEATURES OF DIGITALIS-INDUCED PAT c̄ BLOCK

Auricular Rate	*150–200*
P-P Baseline	Iso-electric
A-V Block	Variable 2
P Wave	Upright, diminutive Lead II
P-P Interval	Irregular or Regular
V.P.B.'s	Present
Carotid Sinus Stimulation	A-V Block Increased, Auric. Rate Unchanged
Potassium Administration	Characteristic Response

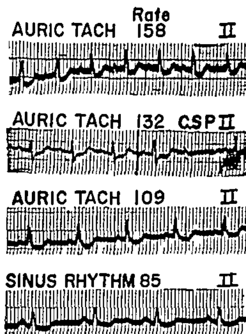


Figure 10 PAT with block simulating sinus tachycardia arrhythmia controlled by discontinuing digitalis and administering potassium

was invariably upright in Leads II and III The P waves in PAT with block usually differed in contour from those present during normal sinus rhythm Unlike flutter or classical auricular tachycardia the P P *interval in successive cycles varied* in duration In some instances the variation was evident to the naked eye A V block was not fixed The response was usually less than 2 1 This accounted for the fact that in the majority of episodes the ventricular rate exceeded 100 per minute Evidence of digtalis intoxication was present in 73% of cases In half the episodes ventricular premature beats were frequent Carotid sinus stimulation or prostigmin administration tended to increase the A V conduction defect while leaving the atrial rate unaltered Potassium administration *induced reversion to normal sinus rhythm* The characteristic sequence of electrocardiographic events during reversion described earlier was noted with but minor variations in all patients

Differentiation from Other Arrhythmias PAT with block is frequently missed entirely or confused with other auricular or ventricular arrhythmias

In the presence of 1 1 auriculoventricular response with an atrial rate less than 150 the disorder may be indistinguishable from sinus tachycardia Figure 10 illustrates one such example The patient s initial electrocardiogram was interpreted as exhibiting sinus tachycardia The presence of diarrhea and yellow vision as well as the fact that the tachycardia followed overdigitalization suggests the presence of PAT with block Application of carotid sinus pressure resulted in a 2 1 atrioventricular response and confirmed this impression Discontinuation of digitalis as well as the administration of small supplements of potassium restored normal sinus rhythm

Three features help differentiate sinus tachycardia from PAT with block First in sinus tachycardia unlike PAT with block where the P waves are of fixed and diminutive size as the rate accelerates the P wave tends to increase in amplitude Second while the P R interval is prolonged in PAT with block it tends to be of short duration in sinus tachycardia Third in the presence of a sinus mechanism carotid sinus pressure does not usually produce A V block In the final analysis a careful scrutiny of clinical events immediately preceding the onset of the tachycardia will provide helpful clues in differentiating the two disorders

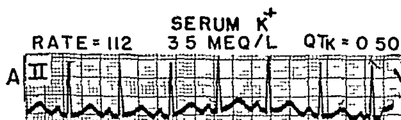
When the rate exceeds 150 per minute with 1 1 atrioventricular response the arrhythmia is usually considered as a supraventricular tachycardia When the P waves are not visible in any of the Leads and when the ventricular rate is slow nodal rhythm is the likely diagnosis Confusion with atrial fibrillation is also frequent The diminutive P wave and the grossly irregular ventricular rate conduce to misinterpretation Many years of continuous fibrillation do not preclude the emergence of PAT with block

PAT with block is most commonly confused with auricular flutter Differentiation on purely electrocardiographic grounds may be difficult or impossible Distinction between the two mechanisms is more than an academic exercise It is of utmost

importance to the patient that correct diagnosis be rendered Opposite therapeutic measures are indicated in the two arrhythmias Digitalis is the drug of choice in atrial flutter and contraindicated in PAT with block Potassium is effective in PAT with block and useless in flutter Generally the patient with flutter is less likely to be in advanced failure and require frequent manipulations of the dose of digitalis or of the diuretic regimen In the majority of instances the electrocardiographic pattern enables distinctions between the two arrhythmias In Figure 11 is shown an electrocardiogram that was misinterpreted as atrial flutter Based on the criteria discussed earlier this is a typical example of PAT with block The atrial rate is 190 the P waves are upright in Leads II and III and separated by an isoelectric base line A V block is variable and ventricular premature beats are interspersed throughout the tracing The arrhythmia developed while this patient was on a constant maintenance dose of digitalis The immediate precipitating factor was a renal potassium losing nephritis The arrhythmia was controlled and its recurrence prevented by the judicious use of oral potassium supplements

Treatment

Discontinuation of digitalis and diuretic agents suffices for the reestablishment of sinus rhythm No additional measures are indicated when the ventricular rate is slow the patient is in good condition or in the presence of renal insufficiency with azotemia Potassium supplementation is advisable when PAT with block develops following diuretic therapy or when the patient is critically ill and the ventricular rate is rapid Potassium may be given by the intravenous route in a dose of 40 milliequivalents diluted in 500 or 1000 cc of 5% glucose and water This amount may be administered in the course of an hour The electrocardiogram must be observed throughout the infusion to make certain that one is not jumping from the frying pan of digitalis intoxication into the fire of potassium poisoning If reversion is partial after this amount more potassium can be given until the process is completed This is demonstrated in Figure 12 The patient whose electrocardiogram is shown was hospitalized because of right and left sided failure The ventricular rate was 120 For several weeks



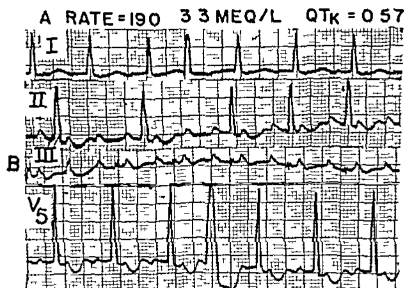


Figure 11 PAT with block confused with atrial flutter in patient with "potassium losing nephritis"

prior to hospitalization he had been receiving cortisone and for a week he had been experiencing anorexia and vomiting Rapid digitalization resulted in gradual acceleration of the atrial rate to 195 At this time PAT with block was clearly apparent Intravenous infusion of 40 milliequivalents of potassium chloride slowed the rate to 180 but did not abolish the arrhythmia An

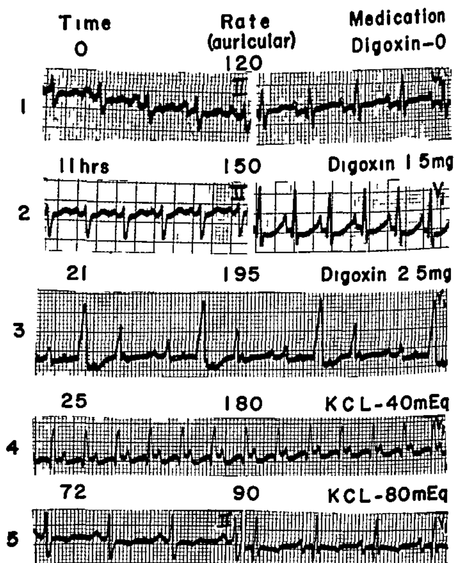


Figure 12 Onset of PAT with block following overdose of Digoxin in potassium depleted patient Arrhythmia controlled by potassium administration

additional dose of 40 milliequivalents of potassium restored both normal sinus rhythm as well as cardiac compensation

In most patients the oral route is adequate Within two hours after ingestion of 5 gm (68 milliequivalents) of potassium chloride slowing of the atrial rate will be evident If reversion is in complete smaller increments may be administered at four hourly intervals until sinus mechanism is re established In elderly patients or those with severe decompensation great caution must be exercised in administering potassium These patients handle potassium poorly and may develop hyperkaliemia even after small amounts

Theoretic Considerations

The clinical data cited indicates that potassium depletion is present in the majority of patients with PAT with block It was further suggested that the loss of potassium preferentially sensitizes the auricles to the toxic action of digitalis This view is based on the following observations In the first place while PAT with block is rarely caused by an overdose of digitalis it is relatively frequently the result of mercurial induced redigitalization In the second place when digitalis intoxication was produced during the extraction of potassium from digitalized uremic patients by the artificial kidney a relatively high incidence of PAT with block was noted It is therefore pertinent to consider the atrial effects of isolated potassium depletion and determine the possible mechanisms which sensitizes the auricles to digitalis

When potassium is removed acutely from dogs by means of hemodialysis while other electrolytes are maintained constant striking changes result in the auricular complex The earliest consequence of such isolated removal of potassium is an increase in the height and width of the P wave with acceleration in the auricular rate The P R interval is simultaneously lengthened with migration of the P wave until it merges with the preceding T wave These changes observed in four different animals are illustrated in Figure 13 In all animals the alterations emerged and receded gradually and both evolution and recession resembled the phases in the onset and offset of PAT with block

What is the mechanism underlying these changes? Impulse

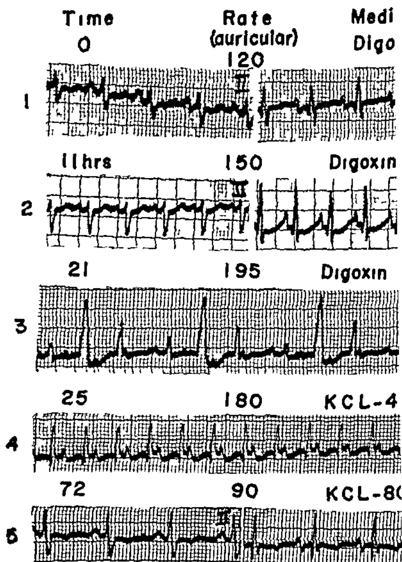


Figure 12 Onset of PAT with block following overdose of Dig potassium depleted patient Arrhythmia controlled by potassium a tration

action of the vagus Potassium deficit does not interfere however with the liberation of vagus neurohumor but merely blocks its effect on the auricles Furthermore the permeability of the cell membrane to cation is controlled in part by the metabolism of acetylcholine It is therefore suggested that potassium deficit may interfere with the action of acetylcholine at the level of the sinus pacemaker but not at the level of A V conduction * In support of this supposition is the observation that in animals with severe depletion of potassium vagal maneuvers will alter A V conduction but not the auricular rate

In what way does potassium deficit modify the action of digitalis? Digitalis has both direct muscular and indirect vagal effects on the auricle These effects are antagonistic on atrial muscle and additive on the A V node Usually the vagal component of digitalis action is dominant In the presence of potassium deficit only the direct auricular action of digitalis would be manifest The direct isolated action of digitalis results in increased automaticity of atrial muscle The result of interference with the vagal effect of digitalis while leaving its direct action unopposed would be an atrial tachycardia with atrioventricular block

If this supposition is correct patients having PAT with block should respond to vagal stimulation solely by alteration in A V conduction This has been the experience When the carotid sinus is stimulated or prostigmin is injected the rate is seldom diminished but A V block is invariably increased Conversely when atropin is administered the rate is seldom increased but A V block is invariably diminished During PAT with block carotid sinus stimulation resulted in second degree heart block without material reduction in atrial rate Several hours later when sinus rhythm was restored by administering potassium the same maneuver did not affect A V conduction but instead caused sinoatrial standstill with nodal escape

If potassium deficit is a prerequisite for the development of PAT with block how is one to explain the episodes which follow

* The arguments for this proposition are fully developed in the monograph "Atrial Arrhythmias due to Digitalis" by Bernard Lown and Harold D Levine (In Press)

DOGS

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Auricular Rates

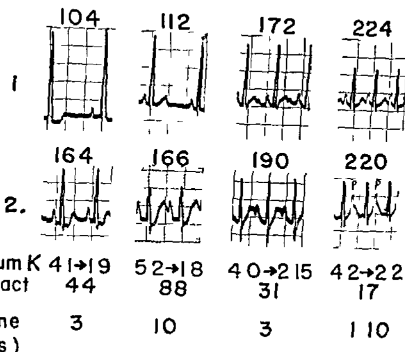


Figure 13 Atrial response in four dogs following selective removal of potassium by means of *hemodialysis* Duration of potassium extraction ranged from seventy minutes to ten hours

formation in the auricles is under continuous vagus control Removal of vagus nerve inhibition on the sinus pacemaker causes waxing in height of the P wave and acceleration in rate comparable to that observed after depletion of body potassium It is known that vagus nerve action is intimately related to the potassium ion Vagus stimulation causes release of potassium from heart muscle Conversely when potassium concentration bathing the heart is increased acetylcholine is liberated When potassium is removed from the perfusing medium of the heart there is a gradual loss of atrial responsiveness to the inhibitory

Panel-Discussion

Moderator E. GREY DIMOND, M.D.

Members of Panel ROBERT BATTERMAN, M.D.
RICHARD BING, M.D.
K. K. CHEN, M.D.
SANTIAGO GRISOLIA, M.D.
BERNARD LOWN, M.D.
ALDO LUISADA, M.D.
WILLIAM SODEMAN, M.D.

MODERATOR I have a large number of questions which have been submitted by our audience We will try to answer and discuss them in a somewhat orderly sequence

MODERATOR Where is digitalis absorbed?

DR CHEN I would say that the absorption in the stomach is negligible it is absorbed principally in the small intestine

MODERATOR Once digitoxin has been absorbed how is it transferred to the heart?

DR BING It is transported bound by plasma proteins particularly albumin Quick acting glycosides such as cedilanid are bound less than a slow acting one such as digitoxin, which is particularly bound to albumin

DR BATTERMAN I would like to modify that slightly Although digitoxin is bound more thoroughly by plasma proteins than the short acting glycosides it is not 100% bound It exists in two forms free and bound with protein

DR LOWN Early clinical studies have indicated that a drug such as cedilanid disappears from the blood within about three minutes

MODERATOR You mean it is cleared by the tissues in three minutes?

DR LOWN Apparently cleared by the tissues Digitoxin will remain in the blood for a longer period An insignificant amount about one per cent will persist in the blood for about ninety six

large doses of digitalis in the absence of loss of body potassium. Much evidence is now available indicating that toxic doses of digitalis promote loss of myocardial potassium. The onset and offset of PAT with block is not correlated to the serum potassium level, but to body deficits of this cation. It may be that depletion of myocardial potassium is a prerequisite for the development of PAT with block.

Summary and Conclusion

PAT with block is usually a digitalis provoked arrhythmia that occurs most frequently in patients with advanced failure who have sustained deficits of potassium. The arrhythmia resembles the changes produced in animals by the removal of body potassium. It is suggested that the loss of potassium inhibits reflex vagal tone on atrial muscle but not on the A V conduction system. In the absence of tonic vagal reflex digitalis enhances auricular muscle automaticity and further promotes the loss of potassium. Thus PAT with block is a digitalis induced disorder caused by auricular sensitization—the result of the vagalytic effect of potassium depletion.

Whether these speculations are validated by further observation and experiment is of little moment. What is of utmost importance is that the clinician begin to recognize PAT with block as a distinct mechanism frequently the result of his own well intentioned but misguided practice.

Panel-Discussion

Moderator	E Grey Dimond M D
Members of Panel	Robert Batterman M D
	Richard Bing M D
	K K Chen M D
	Santiago Grisolia M D
	Bernard Lown M D
	Aldo Luisada M D
	William Sodeman M D

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hours but 50% of the dose is gone within two minutes The binding of digitalis by proteins is not clearly defined

Dr Luisada Do you think there is any action of digitalis on the smooth muscles of the vessels the blood vessels?

Moderator Dr Luisada is referring to several questions but particularly to McMichael s work

Dr Chen I am going to try to answer this question more or less from personal experience in seeing animals and I expect that it would be the same in human subjects When a very large dose is given you can demonstrate vasoconstriction as well as a stimulating effect on the smooth muscle organs such as the small intestines and the uterus However in human subjects you never give a dose sufficient to produce these effects therefore you should not have any physiological activities other than the cardiovascular one

Moderator This question was brought up because at one time McMichael in particular postulated a venous action of digitalis He felt that a principle action of the drug was to increase venous tone and thus restrict venous return

Dr Lown He was using digoxin He based his observation on the fact that ouabain increased cardiac output before changing the venous pressure while with digoxin the cardiotonic action was not immediately apparent but was preceded by changes in ventricular end diastolic and venous pressure the latter he thought primary He ascribed digitalis effect to ventricular decompression the same as achieved by phlebotomy Pooling of blood was believed to occur in splanchnic hepatic areas However Paul Wood injected thorium into animals that were being digitalized and showed there is actual contraction of the liver and spleen immediately after digitalis administration so there was so constriction of the hepatic veins or of the splenic veins Work with catheterization technique has definitely disproved these contentions of McMichael We have observed that when rapidly acting preparations are given intravenously there is a consistent increase in blood pressure However I do not know whether this is the result of action on vasomotor tone or on the myocardium

Moderator There is some work to show an action of digitalis on the carotid sinus Work was done to delineate the site of the

vagal action of sub therapeutic doses When the carotid sinus nerve was resected some of the vagal slowing did not occur thus indicating at least a partial effect on the carotid sinus

Dr Luisada From studies in humans both normal and patients in failure intravenous digitalis medication followed by fluoroscopic and electrokymographic documentation gave us the impression that in the first few minutes particularly from the tenth to the thirtieth minute from the injection there was a decrease in the amplitude of cardiac contractions and we attributed that to decreased venous return possibly due to an extra cardiac action Now if there is such it is probably of secondary importance but it might explain some of the very early effects which are negligible for practical clinical purposes

Moderator Let me ask the panel, do we think there is any extra-cardiac action of digitalis that is important clinically? Do we have any experimental evidence to suggest there is such an action which is significant?

Dr Lown Withering s conception was that the primary site of digitalis action was on the kidney A contemporary of his John Ferriar was the first to suggest that the essential action was upon the heart Since then orientation of clinical attention has been on the cardiovascular apparatus However Gremels in Germany has reopened the question of the action of the digitalis on the kidney In the United States Farber Alexander Pellegrino and Earl * have shown that if digoxin is given to human beings with non cardiac edema there is a slight but definite diuretic action Normal persons who accumulate edema after treatment with large doses of DCA and salt respond to digoxin with a diuresis that is qualitatively and quantitatively similar to that achieved in patients with congestive failure Since in these people there is no significant change in renal or cardiovascular hemodynamics the question comes up whether there is a site of action within the kidney probably on the renal tubule Preliminary observations by Rudolph and Barger at Harvard indicate that when failure was produced in dogs and small amounts of digitalis were given by catheter into one renal artery (amounts of digitalis inadequate to cause a positive inotropic effect upon the heart) a very definite

* Farber S J et al Circulation 4 378 1951

diuresis and sodium outpouring results by the one kidney that had received the digitalis What role this possible extra cardiac action of digitalis has in the treatment of the patient with failure remains to be evaluated

MODERATOR Dr Batterman you mentioned a moment ago that digitoxin is more intimately bound to albumin particularly than are the more rapidly acting substances Is the degree of binding responsible for the delay in therapeutic action? Is that why it is a slower acting form of digitalis?

DR BATTERMAN It probably is It is related to the transportation across cell membranes Perhaps binding with the proteins may delay its penetrating through the cell and also may have some relationship to the toxicity Those glycosides which have a more profound effect on proteins may have a longer persistence of toxicity

MODERATOR Dr Grisolia what is the role of calcium in digitalis metabolism?

DR GRISOLIA Sometime ago there was a paper in a biochemical journal showing that all the calcium in the cardiac cell is in the mitochondria What the significance of this is I do not know

DR BING That would indicate that calcium is of primary importance in energy production and in the oxidative phosphorylation would it not?

DR GRISOLIA I hesitate to draw that conclusion

DR LOWN Dr Solomon at the Harvard Biophysical laboratory is demonstrating that calcium is located in only one part of the red cell and that is the red cell membrane none is present within the cell itself

DR GRISOLIA So far as I know the red cell has no mitochondria

DR BATTERMAN I would like to comment in regard to the utilization of calcium salts in a patient that has been digitalized There have been many comments made regarding the dangers of using calcium associated with digitalis because in animal experiments there seems to be some synergism However one of the classical methods of studying the circulation time in man is the injection of calcium gluconate 10% and it has been used many

times in patients who have been digitalized and there has never been any fatality or any increase in action of the digitalis or calcium in such patients, and I think the fear in man has been grossly exaggerated and is primarily based upon animal experiments

MODERATOR I thought there was one report of a fatality about fifteen years ago

DR BATTERMAN There is a question whether that was due to calcium

MODERATOR Is there anything to suggest that in a person who is fully digitalized and who is not doing well that giving calcium by vein or mouth will produce any augmentation of the digitalis effect?

DR BING In operations on the heart when the rhythm fails or the heart loses tone and everything else fails one tries calcium chloride and I must say that during cardiac operations it has been shown to be quite effective in restoring normal rhythm particularly in the digitalized heart

DR LOWN I have seen similar results When the heart becomes flabby during cardiac surgery or when the heart is in ventricular fibrillation in digitalized or non digitalized patients calcium administration may restore tone and permit defibrillation

MODERATOR Dr Bing in your human studies with coronary sinus catheterization and in whom you measured the gradient in potassium concentration from arterial blood to coronary sinus blood did you study the quantitative potassium difference between therapeutic doses and toxic doses of digitalis?

DR BING We used cedilanid and we only went as high as 1 4 mg. of cedilanid thus we stayed well within the therapeutic range I think Dr Lown had some actual experiments using coronary sinus technique with acetyl strophanthidin

DR LOWN Our work has been with dogs and that does not answer your question It has been found by Hellems and coworkers * that when acetyl strophanthidin is administered within a minute one can detect a coronary sinus arterial potassium gradient which was maximal within six minutes and waned in twenty five minutes Converse but larger exchanges of sodium occurred simultaneously

* H Hems H J Clin Investigation 34 915 1955

MODERATOR A rise in potassium?

DR LOWN Yes a rise in the potassium in the coronary sinus beyond the increase that occurred in the arterial blood This was of significant magnitude If I remember correctly it was of the magnitude of one to two milliequivalents

DR BING It was very statistically significant

MODERATOR So in the dog the administration of a rapid acting digitalis product did cause a release of the potassium from the heart?

DR LOWN Yes

MODERATOR Dr Bing is the potassium content of the intracellular heart muscle the same in a fatigued heart muscle as in a rested muscle?

DR BING That I cannot answer The only way I could answer is in a failing muscle where it is low but in a fatigued muscle I would not know

DR LOWN Fenn in experiments on skeletal muscle has shown that if a muscle is exercised to fatigue cellular potassium is depleted Whether that has any application to the heart has *not been determined The failing heart may be an example of a* fatigued muscle

MODERATOR The chemical structure of digitalis closely resembles that of a steroid Dr Chen do any of the steroids of the adrenal gland closely resemble digitalis in either structure or activity?

DR CHEN Only the steroid ring is common to these substances but there is no lactone ring in the adrenal hormones nor is there any coupling of OH group at C3 and none of these adrenal steroids have a hydroxyl group at C14 and so while they have a structural resemblance there is no identity at all and therefore none of the adrenal steroids has any digitalis like action

MODERATOR Does any product which is active as a digitalis product have to have a hydroxyl radical at C14?

DR CHEN Exactly it must have

DR BING Is the gynocomastia which you see sometimes after digitalis therapy real direct proof of the steroid like character of

the digitalis or is that a secondary response to the digitalis by the adrenal?

DR BATTERMAN I have not seen the gynocomastia

DR LOWN A few years ago in an article in the *New England Journal of Medicine* * gynocomasia was ascribed to digitalis It was based on the observation that some patients in congestive heart failure developed gynocomastia and these patients had normal liver function studies The gynocomastia was ascribed to digitalis but it could as readily been attributed to any number of other factors

MODERATOR Did they perhaps have cardiac cirrhosis with an increase in circulating estrogens?

DR LOWN No they did not have cardiac cirrhosis nor did they have any apparent impairment in liver function

MODERATOR You mentioned Dr Bing a movement of sodium and potassium across the cell membrane What is the source of energy for this pumping mechanism?

DR BING That pumping mechanism which actually occurs in the recovery phase is supposed to be energized by our old friend ATP which was supposed to be the energy source for *everything* until it has been toppled off the throne very recently but energy is apparently not necessary because dinitrophenol and cooling and other enzyme poisons will not interfere with the movement of ions

MODERATOR Dr Chen what is the present U S P standard unit for digitalis?

DR CHEN Previously the standard test animal was the frog and then the cat Presently the official test animal is the pigeon Why? Simply because the different drug firms were buying up the cats at such a rate that no university laboratory could compete the price per cat was $4 00 upwards Besides the pigeon method is just as accurate

MODERATOR In other words it is just as good and cheaper?

DR CHEN Right

DR BATTERMAN I would just like to add a comment here

* LeWinn E B Gynocomastia during digitalis therapy Report of eight additional cases with liver function studies *New England J Med* 248 316 1953

Although it is desirable to have the standardization of any preparation especially as to the impurities there is no correlation clinically between therapeutic effect of digitalis and the U S P unit One unit of digitoxin is equivalent in therapeutic effect to four times the therapeutic effect of one unit of digitalis leaf There is no correlation between the digitalis glycosides and standardization by any U S P method

MODERATOR In other words that factor which is being measured by the U S P method is something quite different than the action we are seeking clinically?

DR BATTERMAN Right

MODERATOR If that is true I do not believe many physicians realize it

MODERATOR Do you believe that a person with severe aortic insufficiency who is still compensated will be kept out of failure longer by being digitalized?

DR BATTERMAN That was Henry Christian s point of view which he brought out some years ago Now it seems clear that decompensation is not something static but is dynamic A patient may be compensated for a certain workload but on over exertion he may decompensate During these periods of decompensation certainly digitalis may be useful The decompensation may occur only during brief periods during the day and in some patients may occur only at nighttime Digitalis may protect such an individual

DR LUISADA This problem applies also to practically every patient with heart disease but who is not in failure For example a pregnant woman with heart disease or a man with severe hypertension (but compensated) might benefit from digitalization

MODERATOR Does digitalis pass into the mother s milk then to the infant?

PANEL MEMBERS I do not know

MODERATOR In animal experiments it has been fairly definitely shown that when toxic doses of digitalis are given to animals that myocardial necrosis may occur Does a similar event occur in human beings if they are heavily over digitalized?

DR BATTERMAN Toxic doses have produced endocardial necrosis and vascularization That has been repeated by Rafael

Gold and Cattell in animals with large intravenous doses but in man I am unaware of any pathological evidence of further damage that results from digitalis toxicity and I have never seen any deterioration of heart disease or any change in the electrocardiogram so I doubt if any damages occur with digitalis toxicity with the usual dosages stopped at the onset of toxicity

DR LOWN This is rather difficult to evaluate In the cardiac patient we have a whole host of pathological derangements To selectively differentiate what is due to digitalis is in the realm of conjecture As to the work in animals receiving large doses of digitalis and having electrocardiographic and eventual pathologic studies the very experiments are of questionable merit If you look through the literature you will note that the animals have been vomiting they have lost weight etc It is very hard to determine whether vitamin or nutritional deficiency or electrolyte derangement are responsible for the lesions I think this question remains moot

MODERATOR Dr Chen is commercial digitoxin obtained from the plant or is it synthetically made?

DR CHEN We obtain it from digitalis purpurea although some yield (much less) can be obtained from digitalis lanata I believe such a product has been made synthetically Actually the chemists have tried to make it but they have not been successful in economically synthesizing this product It is much cheaper to extract it from the leaves of digitalis You know in the early days oh say ten years ago or so there was a fear that digitoxin would be too expensive but I can tell you ten years ago it was a little better than a thousand dollars for an ounce of digitoxin today it is not even one fourth of that amount That amount 1 ounce or 30 gm will make 300 000 0 1 mg tablets Actually the cost of the tablet is in the labor and not in the material

MODERATOR Were any of the digitalis glycosides from Toads ever used clinically?

DR CHEN Some work was done with Bufagin but it is not suitable for clinical use

MODERATOR Is there any clinical significance to the fact that digitalis was once thought to shorten prothrombin time? Is it true?

DR LOWN Actually this has never been confirmed

MODERATOR A patient eighty three years of age with early cardiac decompensation vomits every time she is given digitalis regardless of the form or dose

(1) Is there ever an allergy to digitalis?

(2) Are there occasionally patients who cannot take digitalis no matter how small the dose because of nausea vomiting or arrhythmia?

DR BATTERMAN The allergy of digitalis has only been seen I believe in two instances In both cases the rash was due to digitalis probably because of the impurities that were present By changing the manufacturer's type of digitalis both of these patients were able to take digitalis without any further harm So there is not any real allergy other than these other two cases

In certain patients with advanced rheumatic heart disease any dosage of digitalis preparation may produce a severe arrhythmia I have seen several patients of this type where the smallest dose such as 0 25 mg of digoxin or a fraction of digitoxin or a whole leaf always produced ventricular tachycardia One patient was in a stage of active rheumatic carditis and that patient was carried for a year and a half with mercurial diuretics alone just simply relieving the signs and symptoms of heart failure The carditis finally subsided and she then began to respond to digitalis and took the normal dose without any further arrhythmias

Now turning to the vomiting one has to ascertain whether it is a psychic type of vomiting In that case one has to give the digitalis in some disguised form such as enema or suppository The fully advanced cardiac patient that cannot take any digitalis is somewhat unusual in the practice of medicine

DR LOWN I have seen patients in whom very small doses of digitalis would produce arrhythmias We tried different preparations and they still developed

A Boston physician recently called my attention to a patient who reacts with intoxication if he receives more than 0 25 mg of digoxin every fourth day

I have been skeptical about such reports but I have found that there are patients who are truly sensitive What is the reason for the sensitivity I do not know

DR LUISADA I am very interested in this observation of Dr Lown's I did not know that it would be possible Actually we should emphasize that this is an extreme exception to the average case Perhaps a change in the preparation or a change in the dose or a change in the way of administration would take care of the problem

DR LOWN No we have tried everything I feel strongly that certain patients react to very small doses of digitalis and cannot take the drug I agree that this is extremely rare but should be kept in mind

MODERATOR We have very recently seen such a patient here She is 20 years of age with advanced mitral insufficiency due to rheumatic fever One single dose of gitalin 0 5 mg puts her into ventricular tachycardia each time it is administered

MODERATOR Dr Batterman I gather from what you have said in your formal presentation that you believe that the U S P unit gives no information concerning the therapeutic effectiveness of the drug

DR BATTERMAN That is exactly right There is no correlation between the U S P unit of digitalis leaf or the various glycosides and the effect you can obtain therapeutically in the patient

I would like to give a concrete example of that When the Second World War began the source of American digitalis preparations was cut off very drastically because most of the companies were importing digitalis leaf from England It is the Allen leaf This Allen leaf was more or less standardized for many years and every physician was accustomed to use one and a half grains as representing the one digitalis unit Since the source of supply was cut off other digitalis leaves in this country were investigated and an Oregon leaf was found to have a sufficient amount of active ingredients so that 100 mg was equivalent to one cat unit when given intravenously to a cat When used clinically however this one unit of the Oregon leaf gives twice the effect that was achieved previously with the one unit of the English leaf There is no correlation between the digitalis unit for the leaf and the U S P unit standardization of the glycosides The U S P unit refers only to the quantity necessary to kill the test animal and has nothing to do with the therapeutic effectiveness of the drug

DR LUISADA The method of digitalis standardization was devised twenty or thirty years ago At that time there was no way of producing heart failure in animals This is why they all took as an end point the death of the heart so that actually the cat units and the pigeon units and the frog units were all representing elements of toxicity Now there have been in the last twenty years several methods described on how to produce heart failure in heart lung preparations or in animals I think that it is time for a revision and to introduce a standardized type of heart failure and see how the digitalis preparation overcomes that failure and from that basis establish a new unit

MODERATOR *The U S P unit of digitalis then has nothing to* do with the practice of medicine?

DR BATTERMAN It is merely a guide and help in making the manufacturer adhere to standardization in the manufacture of the drug Even the pure glycosides have to adhere to U S P unitage to assure a certain amount of purity but in the long run when used clinically it has to be in terms of milligrams or gram dosages and the unit has no therapeutic significance

MODERATOR Dr Batterman in your paper you indicated that gitalin has a wider therapeutic range compared with toxic range than other digitalis preparations In other words you believe gitalin is the drug of choice?

DR BATTERMAN In general all preparations have the same action upon the heart and upon all the variables of what can be observed objectively with the possible exception that some have a greater vagal component of action and some have a greater muscular action component However we use the digitalis preparations clinically in the restoration of myocardial efficiency and then qualitatively all the preparations act alike The only difference being that in some glycosides or in some preparations if there is a greater therapeutic range then you may have a decrease in the amount of toxicity with a certain dose but it does not mean that you will have a greater therapeutic effect It means for that particular dose *toxic manifestations will not occur and* then you may extend the usefulness of the preparation but there has been no change whatsoever qualitatively in terms of therapeutic effect

MODERATOR Dr Batterman the margin between therapeutic

results and toxic effect is greater for gitalin than any product that you have tested? Is that true?

DR BATTERMAN So far it is greater in gitalin than any product that I have tried All the glycosides have the same therapeutic range

DR LOWN It is very difficult to maintain a constant clinical state and our own experiences indicated it is extremely difficult to draw clinical impressions utilizing the control of heart failure as the end point Ideally the patient should serve as his own control but the status of the patient changes so markedly from week to week and month to month that it is erroneous to assume that he is a static test object

Now in regard to the results with gitalin our experience has been limited We have found no differences between it and any other drug In looking over the data on which Dr Batterman s conclusions are based it is found that the conclusions are so far unjustified The first report of Batterman DeGraff and co workers is I believe based on forty six ambulatory and 46 bedridden patients The variation in dose of gitalin for toxicity ranged from five to 25 mg This is a 500% difference Within that they discovered a 20% reduction in the therapeutic toxic index A 20% reduction within a 500% range of variability becomes a pea pod in a large lake especially when one considers that there was a similarly large variation in therapeutic dosage

The other point is this they confirmed their conclusions in the following study They doubled the dose of gitalin in twenty seven patients and found that only eleven developed intoxication Eleven out of twenty seven makes a therapeutic toxic ratio of roughly 40% This appears to be a most dubious conclusion For if only four patients are switched to the non intoxication category you get the same therapeutic toxic ratio that has been reported with all the digitalis preparations

It is hard to comprehend why ouabain digoxin digitoxin and all the other digitalis products which have been carefully tested have the same therapeutic toxic ratio as the parent drug itself but this derivative does not Now it may be that this is so but I think the experience represented to date does not validate the conclusion of a different therapeutic toxic ratio

Dr Batterman The studies on gitalin began after a publication on the evaluation of all cardiac glycosides which had been going on in our laboratory for about ten to twelve years We were perturbed about the reports in the literature which indicated that a particular glycoside is one of choice for the treatment of any phase of heart failure We had felt that before that choice was made that one should evaluate every preparation and after twelve years of evaluating the digitalis leaf and digitoxin and lanatoside C and digoxin we published the first paper on therapeutic effectiveness and therapeutic range We pointed out there was not any difference As soon as that paper was published we discovered that much to our chagrin we had neglected one digitalis preparation floating around under the name of gitalin We decided to re do the study and see if we had the same results We followed the same procedures that we used for the other digitalis preparations and within two months we noticed a difference We were not getting the same therapeutic range either both in initial digitalization or in maintenance We were very much perturbed about this We went on and continued our studies and after four years of evaluating under different circumstances we always came up with the same conclusion

The reports that Dr Lown mentioned were the same type of patient that we used for the other glycosides and in some cases they were the same patients Every type of study which is used classically for the evaluation of therapeutic range invariably indicated that gitalin had properties which the other preparations did not so therefore we reported on that particular phase That aroused considerable furor and since then there have been other reports mostly confirmatory There are Weiss and Steigman who came up with the same conclusion Herrmann s group gave a tentative conclusion of confirmation His method however of studying the therapeutic range had no counterpart in the American literature because he used two variables he used the maintenance dose and he used the initial toxic dose and put them together and obtained a new ratio and therefore he concluded that there was not any difference However when done in the classical methods Herrmann s data confirms our own The most important thing whether you believe in the greater therapeutic

range or not is the fact that when a patient has a toxic manifestation from digitoxin digoxin or any other digitalis preparation you want to mention we believe that if you gave an equivalent dose of gitalin you have a chance of continuing the digitalization without the recurrence of toxicity Now it does not occur in every patient but it does frequently enough so that it has its practical points

MODERATOR When you say toxic you are referring to such things as nausea vomiting and not the cardiac arrhythmias?

DR BATTERMAN I am considering every manifestation of digitalis toxicity whether it is cardiac arrhythmias whether it is cerebral toxicity or gastrointestinal toxicity or neurologic toxicity

DR SODEMAN I think it is perfectly obvious from the discussion and from the literature as well one could drink an awful lot of beer in discussing this problem if you wanted to There might be a lot of merit in that if you like beer I do not know whether you are going to settle anything by discussions of this sort at all It seems to me that there is a greater variability in the experimental animal than there is in the product you are trying to deal with and when that is true and that variability gets so great that it is of major importance experimentally as far as the product is concerned you are not going to conclude anything satisfactorily as far as the product goes

DR LOWN The point that needs to be emphasized time and time again is that it does not matter which preparation is used as long as common sense and experience guide its usage One can achieve the same effects with digitalis leaf as one can with most other agents There are a few exceptional situations My own preference has been digoxin the reason being is that I encounter electrolyte problems post surgical patients patients with uremia The rapid action and rapid excretion of digoxin makes it the ideal drug under these circumstances

What is important is to master one drug I think William Withering sort of foresaw this problem when he said The more we multiply the forms of medicine the longer we shall be in ascertaining their proper use and their real dose This is essentially the problem we have now 175 years later The emphasis should not be on the variations in digitalis but rather the vari

ability between patients and in the same patient under different circumstances Respect for the patient in his ever stable instability is the essence of sound therapeutics

DR LUISADA I would like to point out that we have made some progress in a sense of removing some of the variables Now, the first variable was that of the plant Even thirty years ago when we gave an infusion of digitalis we did not know how much of the active glycoside was in the plant We gave a variable dose believing it was the correct substance

The second thing was the manner of preservation The drug which rapidly deteriorated in the hospital now can be maintained at a constant effect simply because it is purified

The third is the way of assimilation Some of these drugs are fully absorbed by the stomach some have other absorption Now we can either give it by mouth or we can give it by injection That is a third variable which we have abolished

DR BATTERMAN Dr Luisada mentioned something in regard to the deterioration of digitalis which I would like to comment upon First of all the deterioration of the crude product is exactly the same as the purified glycoside If it is in a dry state in a tablet there is no deterioration in the life span It is only when it is in a tincture or when it is in an ampoule or when the alkali from the glass plays a role in the oxidation of the glycoside that we have a decrease of potency It is immaterial whether it is pure or whether it is the crude product or whether it is dry it will maintain its potency for many many years

MODERATOR Dr Lown if a patient is in heart failure and in spite of full digitalization remains decompensated can you increase the therapeutic range of digitalis by simultaneously giving potassium? Similarly can you increase the therapeutic toxic ratio by giving potassium?

DR LOWN Our experience to date would indicate and this is very preliminary that potassium may inhibit the toxic effects and that the doses of potassium with which toxicity is inhibited may not interfere with the therapeutic action of digitalis This is a very tentative conclusion However I have had one experience of a patient with atrial fibrillation who was clinically digitalized after receiving a very large dose of potassium she rapidly de

veloped decompensation and had a ventricular rate of 150 per minute whereupon we gave her more digitalis After the potassium action was dissipated she exhibited digitalis intoxication

MODERATOR When you speak of a person being intoxicated and giving them potassium to get them out of the intoxication you are speaking of the cardio-toxic activity?

DR LOWN I am speaking of cardio toxic actions primarily

MODERATOR Do you give potassium for nausea and vomiting?

DR LOWN When a patient has nausea and vomoting we discontinue digitalis or diuretic measures I think that is the simplest and most sound way of treating digitalis intoxication It is mandatory under all circumstances except perhaps when you are dealing with a rapid acting drug like digoxin where you can simply divide and space the dosage It must be emphasized that potassium itself may be a poison This is especially true in patients with advanced chronic heart failure they handle potassium as though they were in renal failure There is not much to be gained in jumping from the frying pan of digitalis intoxication into the fire of potassium poisoning Hecht and co workers have shown that patients with heart failure respond to a large oral dose of potassium with a greater rise in serum potassium level and require a much longer time for urinary excretion of this cation compared to normal individuals

To summarize Patients who have digitalis intoxication demonstrable by ventricular ectopic beats merely stopping digitalis or diuretic measures will suffice For the patients who have more serious disorders such as ventricular tachycardia or advanced A V block or appear to be going downhill I think it is advisable to utilize potassium The administration of potassium will catalyze the change back to normality"

MODERATOR How much is given? How would you give the potassium and what product do you use?

DR LOWN If the patient is hospitalized and there are responsible interns who have time the intravenous route is the safest With continuous electrocardiographic monitoring one can stop the infusion immediately upon the earliest manifestation of toxicity When potassium is given orally one is committed to that particular dose and if it is too much there is trouble

How much is to be used by the intravenous administration? I think 40 milliequivalents in 500 cc of glucose in water is a proper starting dose It can be given in an hour or two and should be followed continually with the electrocardiogram In some this concentration evokes pain it may therefore be diluted to a 1 000 cc of glucose and water and given over a slightly longer interval If one is utilizing the oral dosage 5 gm of potassium chloride serves as an initial dose and followed with smaller amounts at eight hourly intervals Such therapy is to be stopped after intoxication is controlled

I think an additional indication for potassium other than in the presence of established deficit is perhaps for the type of patient that Dr Dimond mentioned earlier who becomes toxic with small amounts of digitalis yet requires it The other indication is in patients who experience mercurial digitalization" In those patients it is worthwhile to give potassium on the day of the diuretic to preclude the development of intoxication

MODERATOR Do you believe in mercurial digitalization ?

DR LOWN I would put it in quotation marks

MODERATOR Do you believe that upon severe diuresis there is a mobilization of digitalis and digitalis intoxication may there fore result? Or do you think the symptoms are due to potassium diuresis?

DR LOWN I think it is more likely that the latter is the critical factor The work of Friedman and co workers is pertinent in this regard These investigators studied the edema fluid of eight car diac patients In four no digitoxin was detected though their embryonic duck heart method is sensitive to 0 05 microgram per cc In the four remaining patients they found 20 micrograms per liter of edema fluid hardly enough to account for redigitalization even after a sizeable diuresis Radioactive distribution studies reveal negligible amounts of digitalis in blood and presumably in edema fluid

DR BATTERMAN The clinical entity of increased signs and symptoms which would suggest over digitalization following the diuresis regardless of whether it is mercurial or aminophyllin or even spontaneous has been reported many times It occurs—at least in the experience that I know—if the patient has been on

digitalis and in the advanced cardiac patients In such patients if you stop the digitalis the day in which the diuretic is given this will be sufficient to avoid the so called *spontaneous redigitalization* Since the amount of potassium loss in either case (when you are giving digitalis or when you do not give digitalis) would be approximately the same following a diuretic I believe that the digitalis must play an appreciable role in the development of these signs and symptoms

Following a diuretic the signs and symptoms of digitalis toxicity can run the gamut The urology manifestations the visual disturbances the gastrointestinal and arrhythmias can occur simultaneously or individually Now I am not aware—perhaps Dr Lown will know—whether potassium restoration will stop the other signs and symptoms such as urologic manifestations visual and so forth

DR LOWN Yes we have seen a number of patients in whom not only the ectopic premature beats or PAT with block responded favorably to potassium but in some subjective manifestations of digitalis overdosage were relieved as well A number of patients felt stronger after potassium Weakness is a common sign of digitalis intoxication as are many neurologic manifestations that are not well appreciated

MODERATOR Do you think that the popularity a few years back of using potassium acid salts instead of ammonium chloride for example might have been partially successful in its use because of this potassium protective action?

I think Dry published a very nice small book on cardiology some fifteen years ago and in that he mentioned the use of potassium nitrate as I recall several grains three times a day as a diuretic

DR LOWN I would repeat that in patients who exhibit digitalis intoxication the judicious use of potassium is advisable always being alert to the hazard of potassium intoxication

DR SODEMAN I would like to ask Dr Lown a point What is the average daily intake of potassium in our normal diet?

DR LOWN On the average daily diet there occurs an intake of roughly 100 milliequivalents of potassium that is the equivalent of 7 5 gm of potassium chloride Potassium is such an ubiquitous

electrolyte that it is very hard to become deficient of it under normal circumstances

DR SODEMAN What are your therapeutic doses as you usually give it by mouth?

DR LOWN Our therapeutic doses are usually 5 to 10 gm in a day That is in addition to the usual dietary intake

MODERATOR What is DeCosta s formula A good for? It contains nitroglycerin gr 1/100 tincture of digitalis 3 minims tincture of strophanthus 1 minim and tincture of belladonna ¼ minim

DR BATTERMAN I am familiar with the product I think it is a gunshot preparation If a patient has a little heart pain and he is a little bit short of breath and has a little stomach ache as many heart patients do instead of giving them three or four different kinds of medication this product combines everything in one and throws in a little extra

MODERATOR Dr Lown you have mentioned several times during this symposium a test utilizing acetyl strophanthidin Tell us the mechanical setup of this how you do it and have you had any fatalities?

DR LOWN Starting with the last question first the answer is yes we have had one fatality in about thirty five tests that we have carried out This fatality occurred at the very inception of our experience

The reason for the test is that occasionally one encounters problem patients in whom it is hard to tell whether the patient has too little or too much digitalis For example the patient may exhibit a bizarre arrhythmia which may simulate PAT with block but does not respond to potassium This test offers an effective and rapid method for deciding the degree of digitalization There are additional exceptional situations which cannot be resolved except by the biologic titration of the patient s digitalis status Of course we do this all the time by increasing or decreasing the digitalis dose Why not then administer digitalis while the patient is being continuously observed electrocardiographically while minute increments are being given utilizing a preparation which is dissipated very rapidly? In addition our experience indicates

that pronestyl will promptly control toxic manifestations of acetyl strophanthidin

Acetyl strophanthidin develops its effect in about thirty seconds and reaches peak action within about five to twelve minutes Toxicity usually does not last longer than thirty minutes and the effect is dissipated within two or three hours We thereby telescope the whole digitalization process while watching the patient for the first evidence of toxicity or therapeutic effect On the basis of this test we decide whether definitive digitaliza tion is indicated or will prove harmful This is roughly the phil osophy of our approach In a number of instances this test has provided information which proved life saving to critically ill patients with advanced heart failure

Dr Sodeman Dr Lown I do not know how many reports there are on this test in the literature but I know of two reports one from the East Coast and one from the West the one from the East Coast saying that the test is dangerous and the other from the West Coast criticizing the test because they felt that you were not using subjective symptoms enough and that you were paying too much attention to the EKG effects Will you comment on these two? I suppose you have read them

Dr Lown Yes I have We emphasized at the time when we first described the test the fact that this an undertaking not devoid of hazard However proceeding with small increments smaller than we had indicated initially we have had no difficulties in some twenty five experiences We did encounter toxicity because that is one of the objectives you are seeking

I think the western study Dr Sodeman refers to was carried out in Portland Oregon by Drs Burgner and David [*] and is reported in *Clinical Research Proceedings* They concluded that the test was valuable They suggested that if acetyl strophan thidin was administered to a limit of *subjective* manifestations they would have a safer test I think they carried out the test on fourteen patients If memory serves they had one death The one death occurred in a moribund patient What has to be recog

[*] Burgner P R and David A Acetyl strophanthidin as a test for degree of digitalization or sensitivity to digitalis *Clin Res Proc* 4 58 1956

nized is that all digitalis *preparations are potentially lethal* In a study carried out on digoxin by Dr Batterman Degraff and Rose † and reported in 1942 they had two deaths In a study which Dr Luisada carried out I think he mentioned one or two deaths In nearly every report testing a new digitalis drug there are some deaths Clinically death due to digitalis is more fre quent than usually recognized Lack of recognition is in part due to the absence of clearly defined and distinctive pathologic lesions The patient *who succumbs to digitalis usually is not deficient in* organic pathology to which death may be ascribed When a drug is given intravenously and full effect develops promptly the patients death is clearly due to the procedure If however a drug is given whose full effect takes many hours to develop the underlying disease rather than the drug is held responsible

Dr Batterman The problem revolves about the reason for the test As I indicated this morning there are a group of patients that you are *not sure are fully digitalized and whether or not the* doses that the patient is taking have an adequate digitalis effect Various schemes have been used in the past to ascertain this fact *One of the earliest* was by one in which an investigator gave a dose of cedilanid intravenously and he claimed at that time that cedilanid was very effective and safe because the majority of patients could take that dose without any serious complications

Years before that Pardee pointed out that ouabain has to be used with extreme caution in patients who have taken digitalis by mouth or who have had any dose of digitalis I believe that the rule still holds that if a patient has any dose of digitalis it is *extremely dangerous to give an intravenous preparation* even though it is very rapidly eliminated because the effects that you achieve in terms of an arrhythmia may be very profound and you can never predict it when you give *that dose Since this particular* test is based primarily to determine whether the patient is fully digitalized it may be safer to use oral preparations which will give you the same endpoint much slower and safer

Now we have had I would say many deaths in using for ex ample cedilanid in patients with advanced heart disease just by

† Rose O A Batterman R C and Degraff A C Clinical studies on Digoxin a purified digitalis glycoside *Am Heart J* 24 435 1942

a single injection of 0 25 mg intravenously The same thing was reported with ouabain using 0 1 mg I think the same principle holds we should not use an intravenous preparation when a patient has had any digitalis no matter how inadequate it was before

MODERATOR Dr Lown although you do carefully observe the patient and you do watch the toxic effects and the desired therapeutic response with your procedure you are really primarily digitalizing to EKG change are you not? Whether it is an arrhythmia or something else your most common end point is an electrocardiographic alteration?

DR LOWN Both electrocardiographic and subjective manifestations of the patient are observed Before proceeding with your question Dr Dimond I would just like to touch on the point raised by Dr Batterman I think it is a good point and needs reemphasis Generally there is no justification for utilizing intravenous digitalis when you can achieve the same result by the oral route Young and enthusiastic physicians at times like to expedite the process of digitalization by giving intravenous medication there is expedition the patient is expedited out of this world The point is that rapid digitalis administration intravenously is fraught with grave hazard irrespective of the type of digitalis employed

Now to return to your question Dr Dimond It is important to decide whether the patient is or is not intoxicated is or is not on an adequate maintenance We utilize acetyl strophanthidin when other methods cannot resolve these problems For example a patient comes in with advanced congestive heart failure and has multi focal ventricular premature beats with nausea and vomiting an enlarged liver and has been off and on multiple digitalis preparations running the gamut from digitoxin to gitalin and at the time the patient is seen it is uncertain whether the patient is or is not digitalized At this point we have occasionally utilized acetyl strophanthidin with very good results We start out with very small increments given at five or ten minute intervals In a number of instances the clinical impression was contradicted and the patient recovered from decompensation by utilizing large amounts of digitalis when all judgment indicated

the patient was in digitalis intoxication Conversely we have had patients with rapid heart action with rates of 190 where the clinician in charge said we have got to give digitalis In these patients the tolerance test indicated that the patient was already severely intoxicated After minute amounts of acetyl strophanthidin bigeminy or ventricular tachycardia emerged The arrhythmias were controlled with pronestyl Thereafter potassium was given with very good results Unrecognized intoxication was thus uncovered

The acetyl strophanthidin tolerance test has a place if utilized by a responsible physician who watches continuously for the earliest manifestations of toxicity One of the important manifestations of acetyl strophanthidin intoxication is change in the contour of the P wave Such a change in the contour of the P wave when associated even with the slightest acceleration of rate may denote severe intoxication and proximity to serious arrhythmia

MODERATOR What are the dosage rates that you have been working with in this product and what are these small increments to which you are referring?

DR LOWN We would start a patient such as I have described who is having multi focal ventricular premature beats with 0 075 to 0 15 mg of acetyl strophanthidin The digitalizing dose ranges from 1 2 to 1 8 mg 0 075 milligrams are given at five minute intervals In a patient in whom it seems likely that he did not have any digitalis or at least an insufficient amount we will start with 0 15 to 0 3 mg assuming than an ampoule contains 0 6 mg

There is one other indication for the use of acetyl strophanthidin other than the tolerance test When a patient presents himself with a supraventricular tachycardia that is not responding to carotid sinus stimulation and other vagal maneuvers (and it is mandatory that these be tried first) one may use acetyl strophanthidin The arrhythmia may be controlled within several minutes If large amounts of digitalis are required the patient is not left with prolonged intoxication

DR BATTERMAN That is a different problem That has nothing to do with the previous digitalization That uses the pharmacological effect of digitalis preparation on the auricular muscle itself and it is a different indication

DR LOWN Would you agree to this that acetyl strophanthidin may be a good drug in such a situation?

DR BATTERMAN Yes I do

MODERATOR What is the clinical usefulness of *urginin*?

DR BATTERMAN I have used urginin extensively both the *maritima* and the *indica* and there is no difference in the action of either one nor in its differences qualitatively from digitalis leaf digitoxin or the other usual glycosides

MODERATOR Classically it is said in the older literature that urginin is one of the products which you can give when other products cannot be tolerated by the patient

DR BATTERMAN It is not so these drugs have the same problems

MODERATOR Are there not references as far back as fifteen years ago by Dr John Sampson of San Francisco reporting that certain arrhythmias were ameliorated by potassium?

DR LOWN Dr Sampson indicated in 1932 that potassium can abolish ectopic premature beats irrespective of cause In 1943 Sampson † and co workers published another paper in which they specifically emphasized the effectiveness of potassium in abolishing ventricular ectopic beats due to digitalis In 1950 Enselberg and co workers again re emphasized that potassium ‡ as well as magnesium § will abolish ventricular ectopic beats

MODERATOR Dr Batterman I understand that gitalin is an amorphous substance and 10 or 20% of it is digitoxin What is the character of the remainder of the residue?

DR BATTERMAN No one knows

MODERATOR Do they know or is it that they just are not talking?

Sampson J J and Anderson E M Treatment of certain cardiac arrhythmias with potassium salts *J A M A* 99 2257 1932

† Sampson J J and Alberton E C and Kondo B Effect on man of potassium administration in relation to digitalis glycosides with special reference to blood serum potassium electrocardiogram and ectopic beats *Am Ht J* 26 164 1943

‡ Enselberg C D Simmons H G and Mintz A A Effects of potassium upon the heart with special reference to possibility of treatment of toxic arrhythmias due to digitalis *Am Heart J* 39 713 1950

§ Enselberg C D Simmons H G and Mintz A A Effects of magnesium upon cardiac arrhythmias *Am Heart J* 39 703 1950

Dr Batterman No one knows When you take the leaf in the dried state and extract it by either of two solvents alcohol or water in one case you have a tincture and the other you have an infusion Even the tincture will have a carry over of an aqueous preparation because no means of extraction is that exact Even digitoxin has gitalin or gitalin fractions in its manufacture Column chromotography studies of gitalin resulted in twelve fractions being identified One of them was digoxin another was gitoxin and ten were an amorphous mixture of all types of materials

Moderator What do you mean when you say an amorphous mixture of all types of materials ?

Dr Batterman No one was able to crystallize it no one knows the chemical structure of it except that each fraction when separated and when injected into animals has a profound digitalis like effect We have taken the ten remaining fractions and removed six of the most potent We know that digitoxin was removed and also gitoxin We treated a series of patients with this purified extract and we had exactly the same results namely of an increased range of therapeutic effect the same as with the impure extract The only difference was instead of 0 5 mg per dose it was 0 3 mg but the same ratio held So whatever fraction is responsible I have not the slightest idea No one knows what the chemical nature is I understand that there are laboratories now at work on this and recent correspondence I have seen has indicated that they may be crystallizing a purified form of glycoside

Moderator Are the products of gitalin now on the market of standard constancy? Can we be certain of their nature?

Dr Batterman I had an aqueous extract prepared by four different companies assuming that I was then able to have a difference in potency but amazingly every lot regardless of manufacture gave the same results and they are interchangeable in the patient and the patient from the point of view of biological variations is unable to distinguish each lot So far as that goes they are equivalent but what is in the mixture nobody knows

Moderator Dr Sodeman should digitalis be used if heart failure is due to acute rheumatic carditis?

Dr Sodeman My answer to that is yes it should be used

The problem in its use I think is a little more difficult than in the usual circumstance In the first place when one uses it under these circumstances the benefits one gets are not as great for reasons which I do not understand The possibility of reaching toxicity is greater and one has to be more concerned about dosage and in watching the patient from day to day but I do believe generally speaking that it is worthwhile to use digitalis in this circumstance I know there are people who do not believe that it ought to be used at all

MODERATOR Very well let us leave the question of acute carditis and take up some general questions

Is the total digitalizing dose related to body weight?

DR BATTERMAN No

DR LOWN No

MODERATOR This is a rather important point to make because many rules for digitalis dosage have used body size as the basic index

For infants such weight rules are probably more applicable

DR BATTERMAN My experience in pediatric patients of course is limited but it has been my feeling that we overemphasize the size of a child As a matter of fact they take a much larger dose they tolerate a much larger dose than one would anticipate I have seen children with rheumatic carditis who surprisingly enough took an adult dose and did very well while if we went on the basis of so many milligrams and so many units per 10 pounds body weight they would be under digitalized

I think the problem in pediatric practice is the same as in the adult that is you give your digitalis until you get the desired effect regardless of size of the patient or unless toxicity occurs

DR LOWN Dr Alexander Davis of the Children s Hospital in Boston has carefully worked out this problem and his results are very interesting He finds that if he divides his pediatric patients at the age of two he notes that above the age of two the requirements are nearly adult in predictability In terms of weight he uses weight or surface area But under the age of two he finds that per pound of body weight they require about nearly twice as much of the drug

MODERATOR Is there any relationship between the cupping and RST *segments and therapeutic digitalization?*

DR BATTERMAN There is a very rough relationship The dose of digitoxin that will produce cupping is about one third the therapeutic dose that is the average therapeutic dose that is required in a series of patients When we compare the various digitalis preparations that are available there is no correllation between the ST and T wave changes and the dosages Some preparations have profound effects and others have no action whatsoever Even with digitalis leaf or with digitoxin in a series of patients the chances of getting significant ST and T wave changes are no greater than 50% There is no correlation with therapeutic index There is nothing in the ST and T wave which indicates toxicity It is an entirely different action and may have no relationship whatsoever to the clinical manifestations of toxicity either subjectively or in the development of premature systoles or arrhythmia

DR LOWN I agree completely with Dr Batterman about the relationship between digitalis intoxication and electrocardiographic significance of ST and T wave changes There is too much reliance placed on the electrocardiogram as a determinant of how much digitalis the patient has received This is a factor in promoting digitalis intoxication The patient comes into the hospital and the doctor says Lets take an electrocardiogram and see whether the patient has had digitalis Calvin Kay in a review of digitalis in a recent Circulation put it this way (to paraphrase roughly) The fallacies of clinical judgment and of the patients memory are better avoided by means of a telephone call than by means of an electrocardiogram I think this is an apt statement ST and T wave changes do not give you any conception of whether the patient has or has not had digitalis Frequently the so called digitalis pattern is simulated by left ventricular hypertrophy myocardial ischemia electrolyte derangements and at times digitalis intoxication may exist in the absence of all ST T wave changes

MODERATOR We will close this panel discussion You have covered an amazing amount of material and a rest has been earned by all

Index

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DIGITALIS

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